OCTOBER, 1952

The Review of Gastroenterology

OFFICIAL PUBLICATION

NATIONAL GASTROENTEROLOGICAL ASSOCIATION

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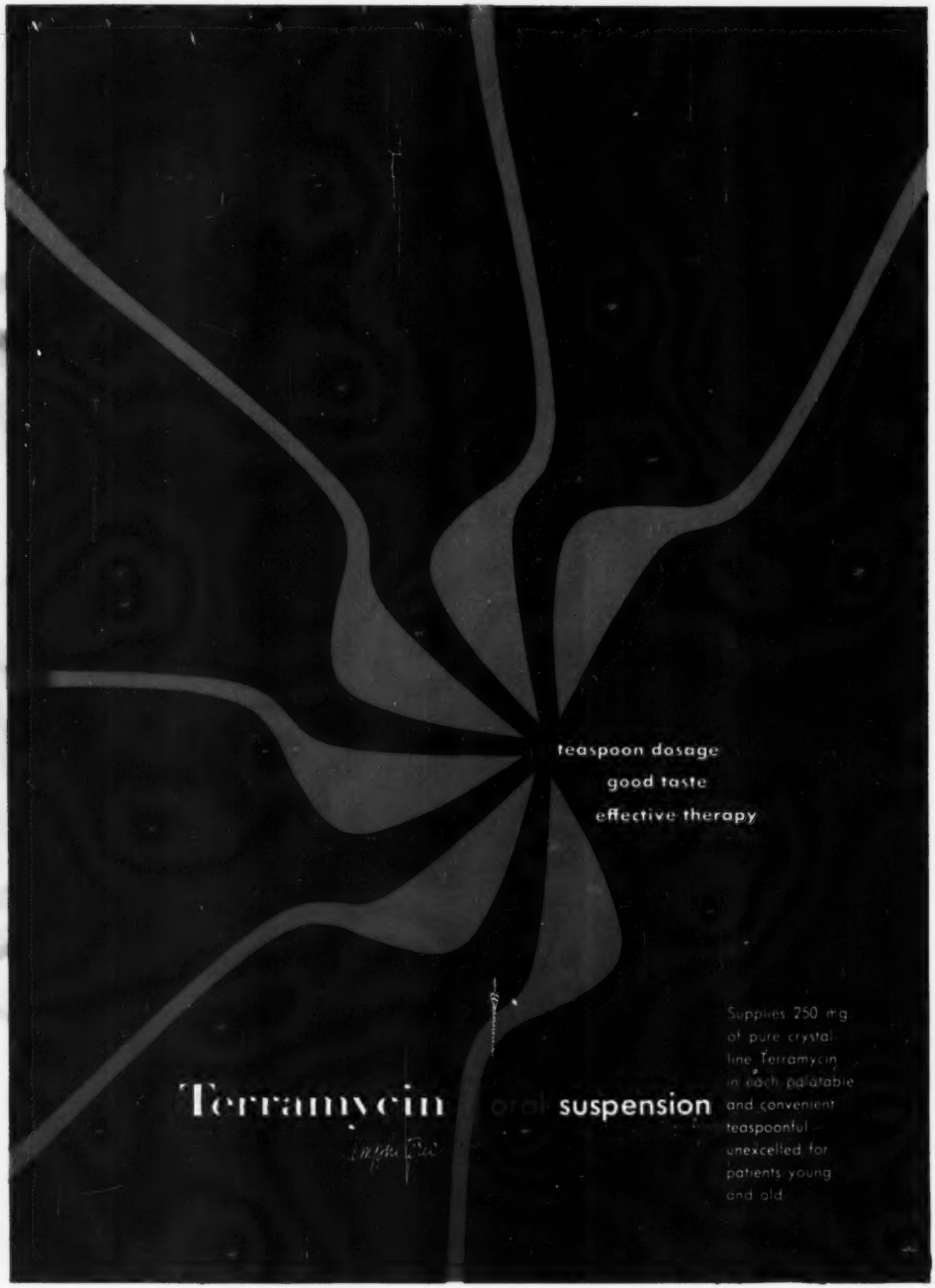
VOLUME 19 NUMBER 10



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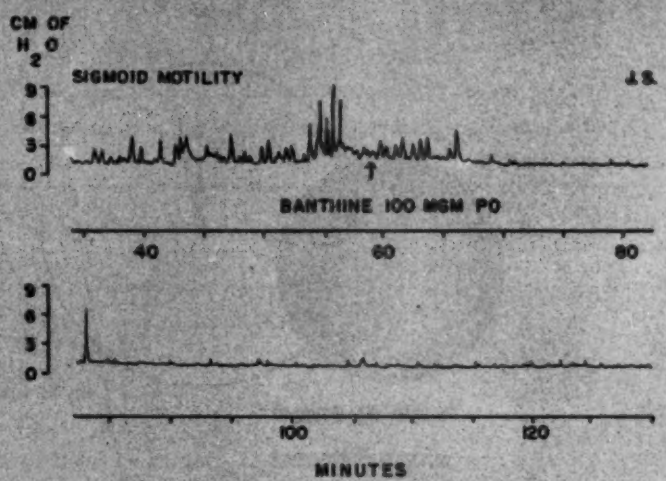

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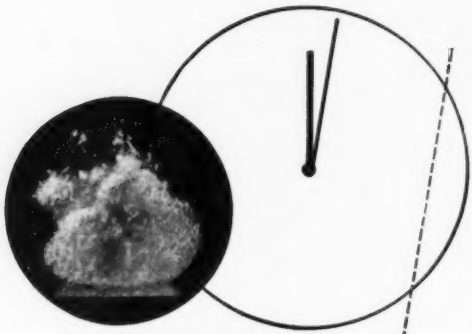

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(INCORPORATING THE AMERICAN JOURNAL OF GASTROENTEROLOGY)

The Pioneer Journal of Gastroenterology, Proctology and Allied Subjects in the United States and Canada

VOLUME 19 OCTOBER, 1952 NUMBER 10

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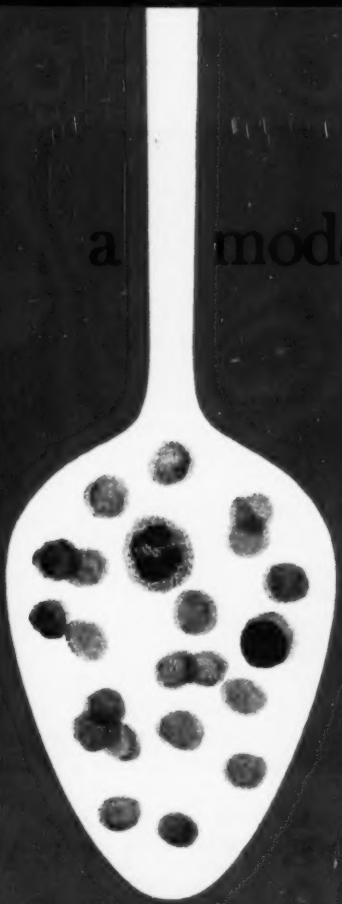

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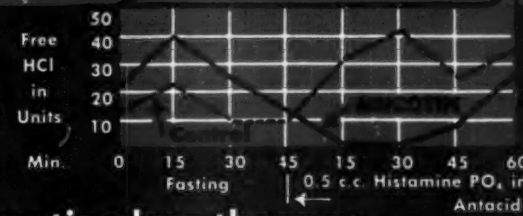

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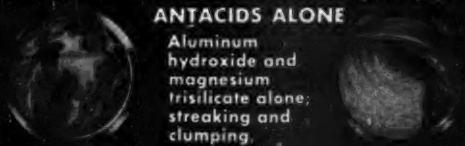

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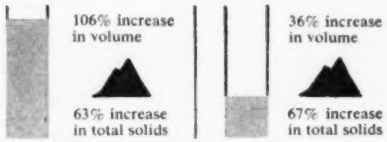

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Volume 19 OCTOBER, 1952 Number 10

TREATMENT OF HEPATIC CIRRHOSIS*

M. A. SPELLBERG, B.S., M.S., M.D., F.A.C.P.†

Chicago, Ill.

The treatment of any disease can be most effectively carried out if we analyze the etiologic and pathogenic factors involved, and cirrhosis of the liver is no exception. This is particularly true about prophylaxis when the most effective therapy should start, but it is also true about active therapy.

The factors involved in the production of chronic, diffuse liver injury characterized by fibrosis, disarranged architecture, and regeneration, i.e. cirrhosis, can be conveniently divided into five groups. Some of these agents may produce acute necrosis which is rapidly fatal. But if their application is gradual and in sublethal doses, but repeated over prolonged periods of time, the chronic cirrhotic stage is attained.

1. Toxins, chemical in nature, have been known for many years to be capable of producing changes in the liver, compatible with a diagnosis of cirrhosis. As many as fifty chemical agents are known to be hepatotoxic and others are being added[142]. It will suffice for our purpose to mention only a few, namely, carbon tetrachloride, phosphorus (yellow), trinitrotoluene and arsenic[111,122,125,134]. Since these agents produce necrosis of the liver, when healing occurs they should be productive of the postnecrotic or toxic type of cirrhosis[9,152], nevertheless the pathologic and the clinical picture may be indistinguishable from portal cirrhosis. Thus the well developed carbon tetrachloride cirrhosis in animals may resemble portal cirrhosis, while Mallory[122] saw typical portal cirrhosis in animals exposed to phosphorus and felt it was of etiologic importance in the human disease. Franklin, Bean and Hardin[72] recently described portal cirrhosis in patients who ingested Fowler's solution for prolonged periods of time.

2. Dietary deficiency, as a cause for hepatic injury and cirrhosis, dates to the observations of Allen and co-workers[4] that depancreatized dogs develop fatty

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†Associate Clinical Professor of Medicine, University of Illinois School of Medicine; Associate Attending Physician, Michael Reese Hospital; Attending Physician, Hines Veterans Administration Hospital.

livers. This was followed in rapid succession by the observations that whole pancreas, lecithin[21,22,87,88] and finally choline[10,19,20] and its analogues[42] would prevent these fatty livers. Others observed that intact rats placed on protein deficient diets would likewise develop fatty livers, and these could in turn be prevented by choline, and methionine, which were termed lipotropic substances[19,23,120]. If these fatty livers were maintained for a long enough period of time, cirrhosis would develop. Cirrhosis was also produced in intact animals on high fat diet[40,175]. In other animal experiments, necrosis and cirrhosis were produced by diet deficient in the B-complex[83], and with excess of cystine[49,59a]; while a choline deficient diet produced fatty changes and later cirrhosis preventible by choline or methionine. Methionine deficient diets would produce necrosis, preventible only by methionine and not by choline[90,93]. More recently hepatic necrosis, and postnecrotic cirrhosis were produced by diet deficient in Vitamin E, (alpha tocopherol) and prevented by this substance[1,80,82,167].

These animal experiments are all the more important since it has been noted that in "alcoholic" cirrhosis in man, the accompanying dietary deficiency rather than alcohol consumption, is of prime etiologic importance[31,44,105,141]. This concept is further strengthened by the frequency of cirrhosis in many parts of the world where alcohol is unknown but malnutrition, (low protein diets) is widespread [75,158].

Proteins, and to a lesser extent, carbohydrates are effective in preventing or reducing liver injury from such toxins as chloroform or arsenic[129,131]. Fats on the other hand were found to accentuate the damage.

Therefore, in summary, it may be stated that diets deficient in proteins, choline, methionine, B-complex or alpha tocopherol are productive of liver injury and cirrhosis.

3. Infectious agents are capable of producing acute and chronic liver injury. Any acute infection or febrile illness can produce some, but usually transient liver damage[34]. The virus or viruses that produce infectious and homologous serum hepatitis can occasionally result in chronic liver disease and cirrhosis [107,175,187,53]. Helminths are capable by lodging in the liver and portal circulation of producing cirrhosis. Schistosomiasis, mansoni and japanicum and Clonorchis sinensis frequently result in cirrhosis but their importance in this part of the world is not great. Malaria and syphilis have been mentioned as etiologic agents in portal cirrhosis[145], but their exact status in this respect is neither clear nor certain.

4. Obstruction to outflow of bile produces the so-called hypertrophic biliary cirrhosis. This may be caused by extrahepatic obstruction of biliary passages or intrahepatic obstruction. The former is amenable to prevention and treatment by surgical means[2,11,24,187].

5. Circulatory disturbances by production of anoxia, and ischemia results in widespread liver injury and may result in atypical cirrhotic process. The circula-

tory disturbance may be due to (1) an occlusion, partial or gradual of one of the main vessels of the liver, the hepatic artery, the hepatic vein, or portal veins[6,7]. (2) Congenital anomaly, patent umbilical veins with production of so-called Cruveilhier-Baumgarten disease[7]. (3) Systemic disturbance of circulation such as occurs in congestive heart failure[29,30,69,103], or thyrotoxicosis[137].

One may question whether the cirrhosis of thyrotoxicosis should be placed under the circulatory heading. Moschcowitz contends that the disturbance is akin to the changes in congestive failure but the defect is a congestion based on increased blood flow. Others (Myers, Brannon, Holland) contend that it is due to a relative anoxia because of insufficient splanchnic blood flow. It is also possible that the increased thyroxin may have a toxic effect on the liver parenchyma or that the increased need for the food stuffs creates a nutritional deficiency.

This brings us to an important point in the pathogenesis and treatment of human cirrhosis, namely that multiple factors are involved in the causation of a given case. A patient may be exposed to a hepatotoxic chemical, suffer from an infection, and ingest a deficient diet. All three factors should be detected and eliminated.

All the aforementioned groups of agents known to produce liver injury should be searched for and if found eliminated, or still better, the prophylactic approach should be used and these agents eliminated before irreparable liver damage results.

Active Treatment

Rest is the oldest, simplest and most effective therapeutic agent in many diseases. It has been referred to as nature's repair shop. In acute diseases of the liver, such as infectious hepatitis, it is probably the most important therapeutic agent, and must be rigidly enforced. In cirrhosis, the institution of rest, and how rigidly it should be carried out depends on the phase of the disease. When the disease is in the inactive stage or compensated stage; when there is no evidence of progression, absolute rest is not necessary, nor desirable. Only slight or moderate reduction in activity may be required. The following symptoms and signs indicate active disease and need for rigid bed rest: Fever, progressive jaundice, marked weakness and tiredness, marked or progressive abnormality of liver function tests, edema and ascites. Bed rest has been prescribed on an empirical basis at first. There is evidence that exercise increases the metabolic demands on the liver, and marked circulatory changes occur in the liver, by merely assuming the upright position[48].

Alcohol

Complete abstinence from alcoholic beverages is usually advised in patients suffering from cirrhosis. However, in view of the fact that there is neither experimental[31,104] nor clinical evidence that alcohol per se[141,183] is responsible for the

liver injury but rather the concomitant malnutrition is the culprit, one may safely permit small amounts of alcoholic drinks if this be stimulating to the patients appetite and increase the food intake.

Diet

The dietary treatment of cirrhosis should begin as soon as the diagnosis is made or suspected. Regardless of the etiologic agent there is enough evidence from the experimental laboratory and clinical observation that a hi-protein diet has a protective effect on the liver. Carbohydrates in abundance are needed. Fat has been shown in animal experiments to be productive of cirrhosis[40,175] and increase the injurious effects of toxins[129,131]. It is true that in these animal experiments there was a shortage of proteins and carbohydrates. In acute hepatitis, some observers have claimed[93a] that fat is not deleterious. Patek and co-workers[146] have successfully used a hi-protein, hi-carbohydrate diet in the treatment of cirrhosis but this group has recently reported the use of a diet containing as much as 175 mg. of fat. This much fat every 24 hours regardless of a possible deleterious effect may not be well tolerated by patients with severe cirrhosis, and may produce dyspepsia of varying degree. For these reasons, we employ a diet containing approximately 150 mg. proteins, 400 gm. of carbohydrates and 100 gm. of fat. The protein contents may be attained by the use of one of the concentrated protein powder preparations on the market. These can be mixed with skimmed milk and flavored to suit the individual taste, or incorporated into jellos, custards, puddings or cereals. The caloric intake is so important that the skill of the dietititian and cook in the preparation of palatable and attractive meals is most important in the therapeutic machinery. For the sake of palatability, we allow the fat content to go up in individual cases.

Parenteral Foodstuffs

If the patient is so ill or has so severe an anorexia that his oral intake is insufficient to meet the above requirements, carbohydrates and proteins may have to be administered intravenously. Glucose can be given in 10 per cent solution in distilled water. Because of the route of administration and the higher blood sugars attained, it is possible to stimulate a damaged liver to greater glycogen storage. (Soskin et al[173]) If given sufficiently slowly little of this is lost in the urine. The administration of insulin may defeat the therapeutic aim by stimulating glycogen storage in the muscle and thus divert it from the liver.

Protein requirements can be met to a certain extent by intravenous administration of amino acids as protein hydrolysate. It is known that the liver deaminizes amino acids and synthesized proteins from them; these functions may be lost in severe hepatic necrosis[59]. In spite of these facts, it has been demonstrated that the cirrhotic liver can utilize amino acids[61,115,161,179,190]. The more completely hydrolyzed, hydrolysates can be used more adequately than the ones containing polypeptydes[37,169]. Although as high a concentration as 15 per cent[5] has been

administered experimentally, in practice 5 per cent protein hydrolysate in 10 per cent glucose is preferable. These should be administered slowly because of the possible production of nausea. Use of saline is avoided because of possible salt retention and as will be elaborated later. It is desirable to administer these solutions after meals because they interfere with oral intake of food by decreasing the appetite and by hampering the use of an arm. The time element makes it difficult to administer more than 1,000 c.c. between meals, that is in an approximate period of four hours, so that if more fluids are administered they inevitably interfere with oral administration. It cannot be overemphasized that the most satisfactory way of meeting the nutritional requirement in health as well as disease, is the oral route. Neither the caloric requirements (only about 1,500 cal. in 3,000 c.c. of 10 per cent glucose with 5 per cent amino acid) nor the requirements for minerals, vitamins, etc., can be so adequately met by the parenteral route.

Plasma can be used to add to the protein needs. This is of particular aid when the plasma proteins are very low. The use of albumin will be discussed later in the treatment of ascites. One should use irradiated plasma to avoid if possible the introduction of the hepatotoxic virus (S-H virus). Plasma is probably not used as efficiently for tissue protein needs as amino acids. The whole proteins have to be broken down to their constituent amino acids before they are used as fuel or resynthesized into tissue proteins[19,37,62,180].

Vitamin Supplements

Vitamin supplements should be administered for the following reasons: They may not be absorbed in normal fashion from foods, there may be a disturbance in their utilization, or they may be required to counteract the cirrhotic process. There is evidence that B-complex deficiency may contribute to hepatic necrosis and cirrhosis. B-complex[12,70,79,51,143,145,146,171] should be administered in adequate dose by mouth in the form of powdered yeast. This may not be tolerated well because about 2 oz. (30 gm.) are required by mouth and an oral concentrate of B-complex can be given instead. The various members of the B-complex can be administered in injectable form, 2 c.c. in daily. Ascorbic acid can be given by mouth 200-400 mg. a day. If a patient cannot take oral feedings because of stupor, the intravenous fluids should be fortified with thiamine chloride 100 mg., niacin 400 mg., ascorbic acid 500 mg. and riboflavin 100 mg.

Vitamin E may be useful in the treatment of postnecrotic cirrhosis in accordance with information obtained from animal experiments[80,82]. Alpha tocopherol should be administered in doses of 200-300 mg. daily. Vitamin A may not be stored or absorbed properly and hence additional Vitamin A, 50,000 to 100,000 c.c. can be administered daily. Cod liver oil, probably because of some of its fatty acid content, may be injurious to the liver of some animals. The need of Vitamin D in cirrhosis is questionable and if indicated can be administered in the form of viosterol.

Lipotropic Agents

The lipotropic effect of choline and methionine is unquestioned in animals on diets deficient in these substances. There is some difference of opinion whether human beings, on a diet adequate in these substances would benefit from their addition in pure form. All agree that if the patient cannot consume a diet sufficiently high in protein, these substances should be administered. According to some inadequate diet is the only indication for lipotropic agents, while an adequate diet without lipotropic agents is effectve in the therapy of cirrhosis[97].

In favor of supplementation is the (experimental) evidence that (1) In liver diseases, methionine excretion in the urine may be higher[86,95]. (2) The rate of its removal from the blood may be slower[101]. (3) Added methionine may have a protein anabolic effect[102]. Choline is reported to be excreted in abnormal amounts in patients with liver damage[38,149]. Moreover, there are a number of clinical studies that indicate improved prognosis and more rapid restitution of hepatic architecture with the use of these agents[15,16,35,135,136,176]. For these reasons, the use of these supplements in clinical cases of cirrhosis are recommended. From the lipotropic point of view, they are likely to be most successful when the liver is large, suggesting a fatty infiltration or, when this condition is proved by liver biopsy. The hard shrunken fibrotic livers are not likely to respond to these agents.

Choline can be used in tablet form or in liquid form as the syrup (syrup of choline dehydrogen citrate 25 per cent sol.) and should be administered in doses of 4-6 grams daily. Methionine in tablet form 3-6 grams daily. These substances are best administered after meals, they are nontoxic but choline may produce diarrhea in an occasional patient. Since both of the above are lipotropic agents, one may question the need for using them together. However, it has been shown that methionine in addition to its lipotropic effect has a protective effect against hepatic necrosis (Himsworth-Glynn) an effect that cannot be attributed to choline. For this reason they may profitably be used together.

Inositol[127, 128] has been shown to have some lipotropic properties but its role in liver disease has not been well established. There are preparations on the market which contain all three of these choline, methionine, and inositol. In this combined form, the dosage of choline and methionine may be too small to be effective. [Methiscol (U. S. Vitamin) 9 capsules=choline dehydrogen citrate 2.5 gram, methionine 1.0 gm., inositol .75 gm.] Cysteine alone has been shown capable of increasing dietary liver injury in animals but combined with choline, it has a lipotropic effect and therefore if used, it should be only in combination with choline.

Liver extract in its crude form has been used for many years empirically in the treatment of liver disease. Later it has been thought to be of value because of its richness in the entire B-complex. More recently a special preparation of liver

extract has been recommended for intravenous use[110]. Finally B_{12} has been found to have a lipotropic effect and have some protective effect against carbon tetrachloride poisoning in animals[56a,80,84,106,139]. The probability is thus evolved that the virtue of liver extract is its B_{12} content or some as yet unknown fraction [56,80,81,84] and if so it may be more efficacious in its purified (15 u/c.c.) than in its crude form[43].

The intravenous form of liver extract therapy (intraheptol) has not appeared to us to be more effective than the old extracts for intramuscular use. We have noticed nausea, anorexia and slight rise of temperature even when it was used with great caution. Therefore, we prefer the intramuscular route. Two to three c.c. of the crude or purified liver extract can be administered intramuscularly every other day and B_{12} 30 micrograms intramuscularly every day. One must emphasize that these agents are not used for their hematopoietic effect.

Endocrine Products

Testosterone:—Evidence of endocrine imbalance is frequently encountered in cirrhosis[118]. Gynecomastia, impotence in the male, pectoral alopecia, female hair distribution, all suggest a possible deficiency of the male sex hormone. In addition biochemical studies indicate an excess of estrogen in the male due to deficient destruction of this hormone by the damaged liver[45,96]. These features suggest the need for male hormone in the male patient. In addition testosterone has protein sparing[100,192] (anabolic) effects while in liver disease, there is a negative nitrogen balance[46] and hypoproteinemia. Thus testosterone should have a favorable effect on the endocrine imbalance as well as on the protein metabolism. It has been used in 25-100 mg. doses three times weekly intramuscularly as testosterone propionate[160]. One of the drawbacks to its use is its possible effect on sodium and water retention. Rosenak, Moses and Howell[159] deny that its use in 50 mg. doses thrice weekly produced water retention in six cirrhotics with ascites and edema.

The varied use to which adrenocorticotrophic (ACTH) and adrenal cortical hormones (cortisone, compound E) have been put in recent years made it inevitable that these substances should be tried in liver disease. The basis for the use of these hormones in patients with liver disease is not sound. Adrenalectomized animals on a high protein diet show more rapid regeneration after partial hepatectomy than normal animals[55]. Adrenalectomy decreases fat deposition in liver[14,17]. Adrenal cortical hormones cause negative nitrogen balance[65] and sodium retention. In liver disease, there is a decrease of sodium in the sweat and saliva as well as in the urine which are evidences of increase of adrenal desoxycorticosterone-like hormones[32].

Favoring the use of these hormones is their property to stimulate the appetite (which may be only a compensatory effect to prevent negative nitrogen balance) and to increase glyconeogenesis. Schwartz[167] has noted that cortisone has an

inhibitory effect on dietary liver degeneration in the rat, and this is due to its glyconeiogenetic property.

The use of these hormones in patients is extremely limited. Webster[188] reported favorable results with the use of adrenal cortical extract, but he also noted the deleterious effects of sodium and water retention. Fink and Williams[71] saw no beneficial effect on the liver from ACTH. A fall of gamma globulin and a favorable effect on pruritus was seen in one case. When used in hepatitis, marked water retention and ascites were noted which necessitated its discontinuance. It has been suggested that minute doses of ACTH 5 mg. per day intravenously may avoid the deleterious effects and produce a desirable result. The only conclusion that one can come to at the present time is that the use of these hormones in liver diseases is fraught with danger, is of unproven values and should await further investigation.

Treatment of Isolated Signs and Symptoms

Central nervous system symptoms in liver disease such as marked restlessness, confusion, changes in personality are of serious prognostic significance. They are forerunners of delirium and coma which frequently precede death. The treatment of mild restlessness and insomnia should be carried out with great caution in cirrhosis. Because the liver detoxifies, barbiturates and opiates, these patients are abnormally sensitive to them, and may sink into coma from small doses. Such tragic results are all too common when an enthusiastic but poorly informed house physician administers a potent dose of barbiturate to a restless patient with cirrhosis. The barbiturates and opiates should be avoided completely if possible, although a small dose of barbital which is excreted chiefly by the kidney may be tried. The bromides preferably the potassium or ammonium salts are preferable to the sodium, which may induce water retention.

Paraldehyde and chloral hydrate may also be used in small doses even though they may have some hepatotoxic effect[77]. Sometimes the use of scopalomine alone may allay restlessness.

Hepatic coma should be treated vigorously although the outcome is usually hopeless. Parenteral fluids, glucose, and large doses of the water soluble vitamins should be administered intravenously. In addition to these it has recently been proposed that aureomycin may have a favorable effect on severe liver necrosis[85] and hepatitis[168]. There is suggestive evidence from the laboratory that aureomycin may have a protective effect on animals placed on a necrotogenic diet. It has been further suggested that this protective effect may depend upon sterilization of the gastrointestinal tract by the antibiotic and thus reducing the absorption of toxic by products of bacterial fermentation and their subsequent delivery to the liver. This explanation is supported by the fact that streptomycin and terramycin have similar but not as powerful an effect as aureomycin while chloromycetin, penicillin and polymyxin are inactive in this respect[80].

Aureomycin can be used in doses of 0.5 gm. q. 6 hours orally or 0.25 gm. q. 6 hours parenterally. Even by the latter route of administration, the antibiotic reaches the gastrointestinal tract through the biliary passages. The clinical results from its use are not impressive. Even if the patient is temporarily rescued from the coma, death may still occur.

Antibiotics should of course be used for the treatment of any superimposed infection. These patients with their poor protein balance have a low resistance to infection and frequently succumb to them. With the advent of the potent antibiotics, this danger has been minimized. Any antibiotic indicated may be used, including the sulfonamides. The toxic effect of the latter on the liver has been greatly exaggerated, they have been shown to have a protective action against certain types of liver injury[194]. One must keep in mind when oral antibiotics are used for any length of time Vitamin K synthesis in the intestinal tract may be impaired, with resultant hypoprothrombinemia. Also change of the bacterial flora may destroy the organisms that reduce the bilirubin to urobilinogen and the latter substances may no longer be detected in the urine or stools[164].

Spontaneous hypoprothrombinemia is not uncommon in severe liver disease, and is usually a late manifestation. Vitamin K administration may not be effective because the damaged liver is unable to synthesize prothrombin. Nevertheless, Vitamin K should be administered daily in about 20 mg. doses. Excessively large amounts of Vitamin K may have a paradoxical effect and lower the plasma prothrombin[182]. Natural Vitamin K may be more effective than the synthetic substances (menadione)[155].

If hypoprothrombinemia is severe, it does not respond to Vitamin K, and bleeding tendencies supervene. Blood transfusions may be the only effective measure.

Anemia, if severe, has a deleterious effect on the entire organism but especially on the damaged liver, by increasing anoxia[53]. The anemia may be due to (1) bleeding from esophageal varices or hypoprothrombinemia; (2) a hemolytic factor has been found in some cases; (3) macrocytic[138] anemia is occasionally seen and has been attributed incorrectly to defective storage of anti-anemic factor[165,193] to reticulocytosis and unknown (toxic) disturbance in bone marrow[18,130]; (4) defective iron metabolism. The anemia may occasionally be more apparent than real, for in view of the increased blood volume, if the cell mass is not proportionately decreased, it will be diluted and appear as an anemia[14]. If the anemia is severe blood transfusions should be used but not to excess if esophageal varices are present.

Exsanguino-transfusions have been used by Snapper and Schaeffer[170] in two cases of hepatorenal syndrome with satisfactory results. Oxygen should be given for the slightest evidence of anoxia to which the damaged liver is very sensitive.

Treatment of Complications

Ascites is one of the troublesome complications and requires skill and perseverance for its successful treatment. A brief discussion of its pathogenesis will clarify the therapeutic measures employed.

In the pathogenesis of ascites the following factors have been incriminated:

1. Portal hypertension
2. Hypoproteinemia, (hypoalbuminemia)
3. Increase of antidiuretic factor and adrenal corticoids which cause
4. Sodium and water retention
5. Increased lymph flow and capillary fragility can be related to the portal hypertension.

1. Portal hypertension although contributing to the formation of ascites is certainly not the sole or most important factor. It is not essential for the formation of ascites in the dog. Ligation of the portal and abdominal vena cava in the dog does not result in ascites unless plasmapheresis is done to reduce the plasma proteins[184].

In human cirrhosis high portal pressure with esophageal varices are reported in the absence of ascites. It is common knowledge that esophageal varices which are always due to increased portal pressure are frequently seen in the absence of ascites. The latter occurring following a drop of plasma protein subsequent to a hemorrhage. Since portal hypertension apparently plays a minor role in the production of ascites, a direct attack on the portal circulation is unjustified for the treatment of ascites.

2. Hypoproteinemia or rather the hypoalbuminemia with concomitant drop in osmotic pressure of plasma may have a decisive effect on ascites formation. It was mentioned in the last paragraph that when protein deficiency is added to increased portal pressure ascites follows. Some deny that there is a direct correlation between the plasma proteins and ascites[144], and others maintain that there is a critical blood osmotic pressure below which ascites invariably forms[25,89].

When the oral administration of proteins is not effective in raising the serum proteins, administration of whole proteins in the form of plasma or better as pure serum albumin is advisable. The concentrated salt free serum albumin is advised. Favorable results on edema, ascites and even liver function tests, and hepatic coma have been reported[8,67,98,108,154,181] from this. Kark and co-workers[98] claim that in addition to the favorable improvement in the plasma osmotic pressure, the increased protein stored in the cells of the capillaries forms an osmotic barrier against fluid, salt and protein leakage. Post and co-workers[156] advise the use of one unit 25 gm. per 100 c.c. first day and increased to 50 mg. a day thereafter. While diuresis may occur the first week, 600-700 mg. may be required for significant effect. If no results are obtained from this amount of albumin, the case

may be judged nonresponsive to this form of therapy. Armstrong[8] has suggested removing the ascitic fluid to dryness and following this by injection of albumin.

The disadvantages of serum albumin therapy are three fold: (1) It does not always rid the patient of ascites even though it raises the plasma albumin and osmotic pressure[67,123,144]; (2) it may produce serious complications such as pulmonary edema[186] and precipitate bleeding from esophageal varices and (3) it is very expensive.

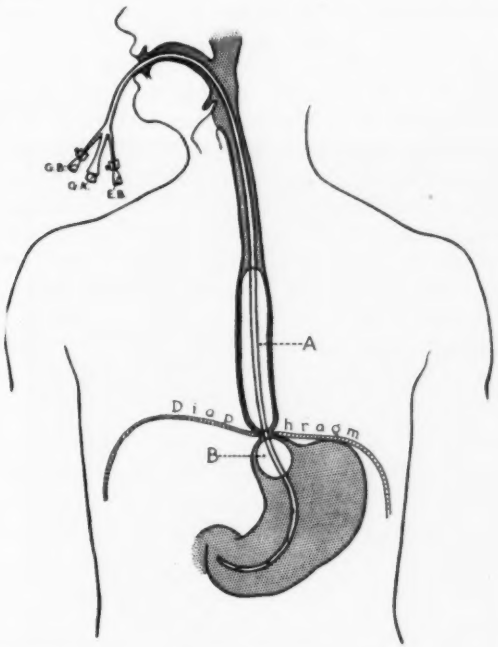

Fig. 1–Sengstaken tube *in situ* with balloons inflated.
G.B. – gastric balloon. E.B. – esophageal balloon. G.A. – gastric aspiration.
A – esophageal balloon.
B – gastric balloon.

Antidiuretic Factor

A tendency for water retention in liver disease is well established. There is an increase in blood volume which is due to increase of plasma volume and not the cell volume. Production of experimental liver damage in dogs is accompanied by water retention when subjected to water tolerance test[3]. Studies of blood volume, extracellular fluid space, and water tolerance tests in acute liver disease by Labby and Hoagland[109], all pointed to water retention. The urine of patients with cirrhosis and ascites has been demonstrated to have an antidiuretic effect[157].

An endocrine imbalance with an increase of a posterior pituitary antidiuretic hormone is therefore a plausible theory[98].

We cannot counteract the hormonal defect directly, but water restriction has been advised in cirrhosis especially with ascites and edema. A maximum intake of 2,000 c.c. of water for 24 hours has been advised. However, it has been suggested by Layne and Schemm[113] that with sodium restriction a high 3,000-5,000 water intake helps to produce diuresis.

Sodium Retention

The hormonal antidiuretic activity operates by stimulating not directly by retaining water but tubular absorption of sodium and water[78]. Urinary excretion of sodium is extremely low even on a liberal sodium intake[6,3,64]. For these reasons, restriction of sodium intake to 200-500 mg. per day has been advised [63,54,98,119]. Since the greater restriction may be too difficult for patients to maintain the restriction, 500 mg. may be tried at first and if no diuresis results further restriction may be attempted. Salt restriction has been shown to be of definite value in producing diuresis and reducing ascites. When extreme salt restriction is attempted the protein rations may have to be supplemented by protein concentrates such as lonalac (Mead-Johnson) delco's granules (Sharpe & Dohme) melactin (Squibb) protinal (National Drug). One of the salt substitutes may be used to improve the palatability of the food.

In addition to low salt diet, sodium and water excretion may be stimulated by means of ammonium chloride administration 1.0 gm. three or four times a day, and mercurial diuretics. The latter should be used sparingly because the mercury of these compounds may have a deleterious effect on an already damaged liver.

As a substitute for the use of a low salt diet which is unpalatable, the ion exchange resins have come into use for reducing the sodium intake in various diseases where such management is indicated[105,117a]. A mixture of acid and potassium resin has been used to prevent hypopotassemia[124]. Sixty gm. of this resin mixture is administered in water in divided doses along with a diet containing 1.5-3.0 gm. of sodium. Most patients prefer this regimen to the extreme salt restriction even though the resin is unpalatable. Because of its unpalatability, it should be administered after meals to eliminate an anorexic effect. The CO_2 combining power of the blood should be watched. The sodium content of the blood should also be watched with all these sodium depletion regimens, to avoid the serious salt depletion syndrome[166], especially when paracenthesis is also resorted to.

Paracenthesis should be used infrequently, chiefly for the purpose of giving patient symtopmatic relief from extreme dyspnea or pain. The removal of large amounts of ascitic fluid results in further protein depletion[121] and prompt reaccumulation of the fluid, unless albumin injections are used concomitantly as

advised by Armstrong[81]. The reinjection of the ascitic fluid, when high in protein, has been advised but with the easier access of protein for intravenous use, this is hardly necessary.

Esophageal varix, is the most serious complication of cirrhosis and second only to liver failure as a direct cause of death in this disease. Unlike ascites the cause of esophageal varices is the increased portal pressure, resulting in increase of pressure in the coronary veins of the stomach, which in turn anastomose with esophageal plexus[74]. These events can be expressed diagramatically:

Portal pressure ↑ coronary vein pressure ↑ esophageal venous plexus pressure ↑ hemorrhage.

Fig. 2—X-ray of stomach showing varices in fundus.

The increased venous pressure in esophageal plexus results in submucosal varicosities which are subject to trauma of the passing food, thermal injury and chemical injury by the acid-pepsin of the stomach[13,185], ulceration with subsequent hemorrhage results. The marked increase of portal pressure which may be 3-4 times the normal value[26,27,162] is transmitted to the esophageal varices and the stage is set for catastrophe.

Like in other complications the best time to meet them is before they occur. Early and vigorous treatment of cirrhosis may forestall this vicious cycle of events. When varices have developed their treatment must be persistent because not only

are they frequent causes of death in cirrhosis but are next in frequency to peptic ulcer as a cause for upper gastrointestinal hemorrhage.

The treatment of esophageal varices may be directed toward the varices themselves and consist of the following:

1. Injection of sclerotic agents
2. Balloon compression of varices
3. Ligation of submucosal veins
4. Resection of vein bearing area
5. Ligation of coronary veins of stomach.

Injection of sclerosing agents (Sod. Mohuate 5 per cent) into varicosities through an esophagoscope has been introduced into this country by Moersch in 1940[132]. This has been done even during the period of bleeding without untoward results with stoppage of hemorrhage[133,147,189]. Hemorrhage, however, has frequently recurred and hence this procedure offers no lasting protection.

The emergency treatment of bleeding esophageal varices by balloon compression was suggested by Rowntree and co-workers[163]. Later a triple barrel, double balloon tube was proposed by Sengstaken[167a] (Fig. 1). The tube is inserted through the nose into the stomach to the 55 cm. mark. The gastric balloon is inflated with 100 c.c. of air and the entire tube drawn back till it is stopped by the cardiac sphincter. The tube is fixed at this point and the esophageal balloon is inflated to a pressure of 20-30 cm. of mercury. This pressure is sufficient to compress the esophageal veins and stop the hemorrhage. Suction can be maintained on the gastric tip of the tube. When bloody material is no longer aspirated, it is proof that the bleeding has been stopped. If the bleeding does not stop in spite of maintenance of sufficient pressure in the esophageal balloon, with the balloon in the proper location, there is a probability that there is also erosion and hemorrhage from dilated veins in the fundus of the stomach. It may be possible to compress these by further inflation of the gastric balloon (200 c.c. of air or more) and pulling it lightly against the diaphragm. This procedure has not been successful in our hands. Bleeding gastric varicocities are a frequent cause of failure of this method (Fig. 2).

When the bleeding veins are effectively compressed, the tube should be left *in situ*, with continuous inflation of the esophageal balloon, for at least 48 hours. The balloon is then gradually deflated if the bleeding does not recur the entire apparatus can be removed. While the tube is *in situ*, the patient can receive liquid feedings injected, through the gastric tube. This is a valuable supplement to the intravenous fluids.

Blood transfusions should be given to compensate for the loss of blood but these should be given slowly and in limited amounts. No attempt should be made to attain a normal blood count but one should be satisfied with a blood count

of 3.5 ml. or slightly above, because the increased blood volume will increase the portal pressure and set the stage for further bleeding. This cautious attitude must be maintained in spite of the known sensitivity of the liver to anoxia, and the danger of developing ascites from the lowered plasma proteins. One must cautiously walk the narrow plank between two precipices.

Crile[47] performed transesophageal ligation of submucosal veins after surgical exposure of the esophagus. All seven patients apparently had an extrahepatic portal vein block. Phemister and Humphreys[150] reported the resection of vein

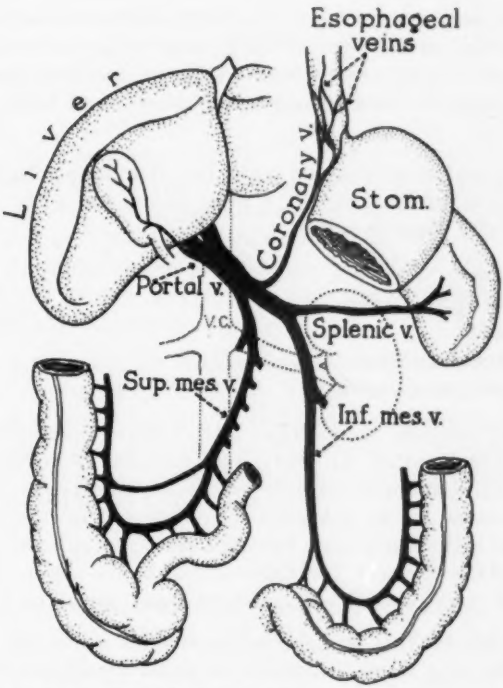

Fig. 3—Diagramatic scheme of portal vein, its tributaries and important anatomical relationships.

bearing area in two cases of bleeding esophageal varices where other methods of therapy failed. This consists of resection of distal esophagus and fundus of stomach (esophageal plexus and coronary veins) it is a very extensive procedure with a good deal of surgical risk and should be reserved only for those cases where other procedures, especially shunt operations, have failed. Ligation of coronary veins of stomach will remove the chief source of blood to the dilated esophageal plexus and thereby temporarily reduce their pressure. This is a

palliative procedure for eventually these channels are re-established in the presence of the continued high portal pressure.

Procedures to change or improve the collateral circulation is the oldest surgical procedure and dates back to Talma[178] and Morrison[135] who introduced omentopexy, a procedure that still carries their names. This operation is chiefly of historical interest, newer and more effective methods have replaced it. Cates[39] reported a series of patients in 1943 with a mortality of 42 per cent in two weeks after omentopexy. In addition to its high mortality, it rarely accomplishes the aim of the procedure.

The surgical production of a posterior mediastinitis to divert the blood from the submucosal veins to the posterior mediastinal veins has been proposed, by Som and Garlock[172]. It apparently relieved the recurrent hemorrhage in their two cases. This seems to be a procedure too drastic, and hazardous for widespread use.

Operations aimed at reduction of portal hypertension by direct attack on the portal vein or its tributaries (Fig. 3) is more sound and in this group, are the procedures of choice. These include:

1. Splenectomy
2. Ligation of splenic artery
3. Portal shunts
   a. splenorenal anastomosis
   b. portacaval anastomosis

Splenectomy[58] removes about 40 per cent of blood entering the portal veins and therefore, should reduce the portal vein pressure. Moreover, the enlarged spleen may produce thrombocytopenia and leukopenia (hypersplenism), both of these are overcome by the splenectomy. Ligation of splenic artery is a very simple procedure and accomplishes the same results as splenectomy by the resultant atrophy of the spleen[166]. The above attacks on the spleen, however, forfeit the chance of the more rational and successful shunt operations to be described.

Thus at the present time splenorenal anastomosis is probably the procedure of choice for the long range treatment of portal hypertension which is the immediate cause of bleeding esophageal varices. This operation consists of one stage splenectomy and anastomosis of the splenic vein to the left renal vein which is a tributary of the inferior venacava[26,27,116,117,162]. If the opening is sufficiently large, there is an immediate drop of the portal vein pressure and this lowered pressure persists as long as the shunt remains patent. If this shunt closes and bleeding of the esophageal varices recurs, it is still possible to perform a portacaval shunt, or anastomosis between the portal vein and inferior vena cava, unless there is a cavernous transformation of the portal veins[28,116,117,148]. This is however, usually not the case in portal hypertension due to intrahepatic obstruction (cirrhosis).

The evidence accumulated so far favors these shunt procedures as most successful for the treatment of bleeding esophageal varices. The two questions to be answered are: (1) will these shunt procedures remain patent and (2) will this procedure (really an Eck fistula) have a deleterious effect on liver function?

The answer to the first question derived from animal experiments is not favorable. Douglas and Nichu have shown that portacaval shunts in dogs close in 3-6 weeks in ⅓ of animals. The increased portal pressure in patients, however, would help to keep it open. Nevertheless in human beings these shunts have closed, but this has been attributed to the small openings.

In answer to the second question, there is evidence from the laboratory that Eck fistula dogs are deficient in producing plasma proteins and hemoglobin (Whipple, et al) and that there is decreased dye clearance in dogs after portacaval anastomosis. The latter, however, may be due to decreased hepatic circulation. In human beings, Bradley[33] has shown that after shunt operations, the estimated hepatic blood flow (EHBF) decreased consistently. It is therefore likely that a further decrease in hepatic blood flow to an already impaired liver may result in further injury. Indeed, not infrequently, several months postoperatively, some of these patients may become jaundiced and go into hepatic failure. This, in addition to the considerable surgical mortality, means that these procedures should not be done for the presence of varices alone, unless one hemorrhage has already occurred.

The immediate treatment of esophageal hemorrhage before the more definitive treatment, consists of the following: (1) Absolute bed rest; (2) Trendelenburg position (has been advised to decrease pressure in the esophageal plexuses); (3) only cool liquids by mouth or nothing by mouth; (4) mild sedative; (5) blood transfusion given slowly unless the patient is in shock; (6) insertion of esophageal balloon and compression of bleeding varices.

Summary

1. The treatment of cirrhosis of liver is discussed with regard to the five large etiologic factors (a) toxins (b) dietary deficiencies (c) infectious agents (d) biliary obstruction and (e) circulatory disturbances.

2. The rationale of high protein diet and supplements of lipotropic agents, vitamins, liver extract, B_{12} is pointed out.

3. The pitfalls of the treatment of certain symptoms is emphasized.

4. The pathogenesis of ascites and bleeding esophageal varices and their modern treatment is discussed.

(Because of lack of space, references will appear in the reprints.)

AN EXPERIMENTAL AND CLINICAL STUDY OF A SYNTHETIC CHOLERETIC*

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For a long time the natives of Dutch India have been using the squeezed juice of a curcuma species (curcuma javanica, Temoe Lawak) diluted with water for the treatment of chronic diseases of the liver. In studies by Koch, Guttenberg, Kalk and Nissen it was established that an infusion of the total extract causes a strong increase of the bile flow in man; in addition, a cholekinetic effect was found to a lesser extent. Dieterle and Kaiser succeeded in identifying chemically the active principles of the Temoe Lawak drug, namely, various coloring substances – among them the curcumin – and an essential oil which in its high boiling fractions contains an alcohol, the paratolylmethyl carbinol. A thorough investigation of the pharmacodynamics of the dye stuff as well as of the paratolylmethyl carbinol by Franquelo, Grabe and Robbers showed that while the coloring substance (curcumin) possesses a typically cholekinetic action, causing a rhythmic evacuation of the gallbladder and yielding a typical dark and viscous bladder bile, the paratolylmethyl carbinol provoked a definite choleresis, a genuine, continuously increased secretion of light liver bile. Studies on rats (a species which do not possess a gallbladder) corroborated the findings in other experiments that the paratolylmethyl carbinol is a true choleretic stimulating the bile secretion by the liver.

The paratolylmethyl carbinol was then synthetized and a water soluble salt was developed – the diethanolamine salt of its camphoric acid ester – permitting the parenteral administration of the drug.

Sieberth investigated the choleretic action of the said salt in man administering the drug intramuscularly and studying its effect by means of the duodenal tube and the double-lumened stomach duodenal tube. In a series of seventeen patients he found that the lowest increase of the bile secretion was of 189 per cent, the highest of 679 per cent of the initial value, the average being of 439 per cent. The choleresis was continuous and even, the color of the bile remained uniformly light.

Kalk studied the effect of the drug by oral administration in 26 patients (8 without liver damage, 8 with gallbladder disease and liver damage, 10 with icterus catarrhalis). In patients with normal liver and bile system 500 mg. of

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the drug caused an increase of the choleresis by 300 per cent of the initial value. Studies in patients with diseases of the liver and bile ducts showed that the more serious the liver damage was the less was the response of the liver to the choleretic stimulation. X-ray studies showed an additional secondary cholekinetic effect. It was shown in comparative experiments with dehydrocholic acid that the choleretic action of the orally administered drug is considerably stronger than that of 10 c.c. of 20 per cent solution of dehydrocholic acid given intravenously. Liver function tests were carried out in 8 patients; in no instance was there any indication of a lesion in the liver parenchyma.

Bruhl reported his findings when treating with the drug 121 patients with diseases of the bile ducts and the liver, 79 with diseases of the bile ducts and 42 with diseases of the liver parenchyma. He found a rapid subsidence of the objective symptoms and subjective complaints. The best effects were obtained in cholangitis.

In this study the drug will be designated by the code name PTMC. The toxicity was studied by Berke, Levenstein and Kleinberg. The acute LD_{50} in rats by subcutaneous administration is 500 to 520 mg. per kilo bodyweight of the animal. In oral administration no toxic effects were observed when up to 5,000 mg. per kilo bodyweight of the animal were administered. Further studies were carried out by Kleinberg: oral administration of up to 3,000 mg. per kilo bodyweight caused no death; subcutaneous administration of 1,250 mg. per kilo bodyweight caused no death; in approximately half of the subcutaneous injections there was a severe necrosis of the skin at the site of the injection; 750 mg. per kilo bodyweight given intraperitoneally caused two deaths out of 5 animals treated; intramuscular injection of 500 mg. per kilo caused no death – there was no necrosis, or any other damage to the tissue at the site of the injection.

Chronic toxicity tests on dogs were carried out by Kleinberg. The animals received by stomach tube 250 mg. of the drug per kilo bodyweight daily, for a period of 100 days.

The weights were observed carefully, blood counts (including differential) and liver function tests were performed periodically; after the experiment the animals were sacrificed and autopsies made.

There was no impairment of appetite and the dogs maintained a normal weight, and the continuous oral administration did not alter the blood picture. There was no impairment of liver function. On autopsy no lesions were found in the gastrointestinal tract, liver and kidneys.

The choleretic effect of PTMC was studied by Kleinberg on chronic bile fistula dogs. A comparison was made between the secreted bile of untreated dogs with that of the same dogs after administration of PTMC. Sodium dehydrocholate was used as a control. The results show that the stimulation of

bile secretion by PTMC is better than the one obtained with sodium dehydrocholate and that such stimulation is not evidenced by increase of concentration, but rather by an increase of the bile. The bile remains essentially normal in composition.

The previous observations and publications abroad and the studies carried out by American observers on the toxicology and pharmacology of the compound induced us to investigate the effect of PTMC* in diseases of the liver and the biliary tract and to evaluate its therapeutic effect in comparison with other choleretic agents.

Experimental

The following two procedures were carried out:

Drainage:—In order to evaluate the efficacy of PTMC and other choleretics, normal human subjects were used. We were careful, when possible, not to give these preparations where we were suspicious that there might be a complete common duct obstruction, or in the presence of a markedly enlarged liver, an acute cholecystopathy or an exacerbation of a previous cholecystopathy.

First Day:—Office, out-patient clinic and hospitalized patients were instructed to appear for examination without breakfast. A size 16F. duodenal tube was passed into the stomach and the gastric contents aspirated and examined chemically and microscopically. Following the aspiration, the stomach was lavaged through the duodenal tube with normal saline solution at body temperature and the patient was instructed to swallow the tube until we obtained an alkaline stringy mucus resembling egg white. Often this mucus was bile-stained or mixed with free bile. To make certain that the tube was in the descending duodenum, air was injected through the tube and the stethoscope placed upon the abdomen in the duodenal area or, when feasible, the location of the duodenal tip was visualized by fluoroscopy. When it was ascertained that the tip of the tube was in positition, gentle aspiration with a Tilden-Brown syringe was done and the aspirate was subjected to chemical and microscopic test. From the time that the tube entered the duodenum and before the first aspirate was obtained, the tube was clamped off for 15 to 20 minutes so as not to allow the escape of any duodenal contents externally. After this period of time, the tube was connected with a drain bottle and the bile was allowed to drain for a period of two to three hours. Each hourly aspirate was collected separately. The quantity obtained in each bottle was charted and examined chemically. This concluded the first day experiment.

Second Day:—The same patients were intubated on a fasting stomach. After the usual preliminary steps it was ascertained that the tube was in the duodenum and a tablet of the choleretic chosen for control was crushed and

*We are indebted for a supply of the drug to Specific Pharmaceuticals, Inc., New York City, where the drug (Olymethol) was synthetized.

suspended in 10 c.c. of warm water and slowly injected through the duodenal tube and washed down with another 10 c.c. of warm water. The tube was clamped and no aspiration was attempted for 15 minutes. After this period, the tube was connected to the drainage bottle and the duodenal contents drained for a three hour period. Each hourly sample was measured and examined as on the preceding day.

Third Day:—Using the same procedure as described above the patients were again intubated and after the preliminary gastric aspiration a suspension of 25 mg. PTMC in 10 c.c. warm water was injected through the duodenal tube and washed down with an additional 10 c.c. of warm water. This was repeated

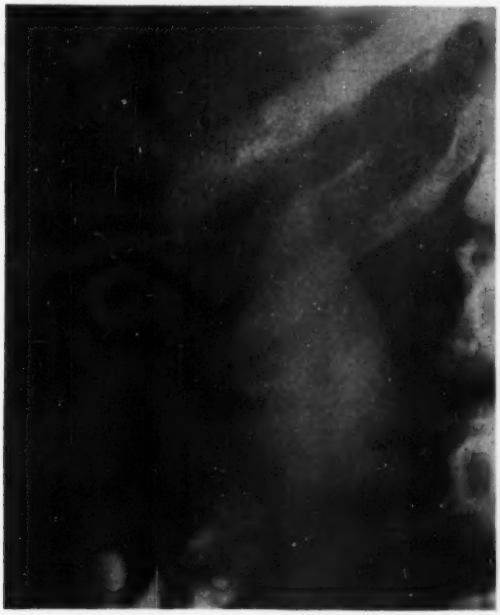

Fig. 1—Biliary drainage, PTMC for three days and 6 Monophen capsules the evening previous to cholecystography. The gallbladder shadow stands out prominently and the liver shadow is more dense.

at half-hour intervals until 75 mg. of the PTMC was given to the patient. Instead of administering single doses as was the case with the control choleretics, PTMC was administered in three divided doses, in order to establish the onset of the choleretic effect and its changes under the influence of the first and subsequent administrations. Each specimen was collected separately and examined chemically and microscopically. The collection of the drained duodenal contents was then continued until attaining the three hour period as described above for the first and second days of the experiment, so that the

duration of the experiment was the same for the first day (no stimulation), the second day (use of a choleretic chosen for control) and the third day (use of PTMC).

These experiments were carried out to ascertain by biliary drainage in the selected patients the amount and kind of bile secured without a choleretic, with a control choleretic and on the third day with PTMC.

In a further series of experiments administration by stomach tube was replaced by oral administration. Both the controls and PTMC were given in comparable doses for three consecutive days and then drainage was performed using the same technic as above described.

Without stimulation the average volume of duodenal bile obtained during a three hour period was between 80 to 100 c.c.; after stimulation with PTMC the average duodenal bile obtained during a three hour period was between 120 and 240 c.c.; these quantities compared favorably with those obtained with the choleretics used for control in this study.

Antispasmodics were given whenever necessary to facilitate the passage of the duodenal tube and/or to overcome a contraction of the sphincter of Oddi; this measure was applied in the control experiments as well as in the PTMC series.

X-rays:—The above described drainage experiments showed that PTMC is a true choleretic increasing the secretion and the flow of bile. Further proof would be obtained if the oral administration of PTMC previous to that of a contrast medium would show certain effects in the subsequent cholecystography. The expected effects on gallbladder shadow would be as follows if PTMC is a choleretic which increases the bile flow:

1. The early and incomplete shadows may be more opaque and larger.
2. The fully developed shadow may be made larger although fainter by the secretion of more bile into the gallbladder.

The objectives of these experiments are twofold:

1. To obtain further proof that PTMC is a choleretic.
2. To show the possible use of PTMC in conjunction with the dye for the visualization of the gallbladder or to deepen the shadow where the collection of bile is slow for any reason.

Patients were chosen in whom cholecystography was performed previously unsuccessfully or with unsatisfactory results. PTMC was given orally during three to five days in doses of 25 mg. to 75 mg. three times daily after meals (daily doses of 75 to 225 mg.). Contrast media (Priodax or Monophen) were given in the evening of the last day of PTMC therapy and cholecystography was performed the next morning. In the great majority of patients treated in this

way it was found that – when using PTMC – the gallbladder was more clearly visualized, the shadow deepened and also the liver was more clearly outlined although previous attempts – without the use of PTMC – to visualize the gallbladder remained unsuccessful.

Figures 1, 2 and 3 show representative cases:

Clinical

We investigated the action of PTMC in 150 patients, male and female. The youngest patient was a high school girl, 16 years of age, who had had several episodes of right upper quadrant distress after indulging in rich foods, eggs,

Fig. 2–In this illustration the gallbladder and the liver are well outlined. In the fundus of the galbladder there are numerous concretions. Biliary drainage and the administration of PTMC and the dye resulted in this photograph.

ice cream, whipped cream and various pastries. The oldest patient was 65 years of age who had had a cholecystectomy about 30 years previously. After careful histories were obtained, these patients were divided into several categories:

Patients who complained of indigestion with belching, heartburn and constipation without definite symptoms referable to the biliary tract.

Patients who complained of indefinite right upper quadrant pressure or sensitiveness occurring several hours after eating.

Patients who gave a history of one or more attacks of pain referable to the right upper quadrant of the abdomen with occasional radiation of the pain to the back with or without shoulder pain.

Patients who had repeated attacks after indiscretions of eating and drinking.

Patients whose attacks were infrequent but on x-ray examination of the gallbladder with the dye, the gallbladder was poorly visualized or not at all.

Patients who showed poor emptying of the gallbladder after the usual fatty meal.

Another series of patients were observed who had been operated on and the gallbadder removed with or without having had stones. Five of these patients have been operated on more than once after the cholecystectomy. Their symptoms were due to stone in the common duct, spasm of the sphincter of Oddi and adhesions. Two patients are walking around with a tube inserted into the common duct. In these two patients PTMC improved the biliary flow, liquefying it and thus relieving the intrahepatic pressure. In the presence of stones in the gallbladder PTMC was used with caution so as not to overstimulate the biliary system and thus bring on an attack.

In all of these patients gastric analysis, biliary drainage, blood counts, blood chemistries, x-ray studies of the gallbladder (except in those patients who had their gallbladders removed) and gastrointestinal tract were routine procedures. In many patients liver function tests were carried out before, during and after PTMC therapy. Never was any impairment of the liver function observed which could have been ascribed to the effect of the PTMC.

A gratifying observation obtained by us was in the patients who complained of indefinite digestive disturbances and in those patients whose gallbladders were poorly visualized or not at all. After several biliary drainings and the oral administration of at least 75 mg. of PTMC, we were able, in most patients, to visualize the gallbladder and at times even the liver shadow seemed to be clearer.

We found that 75 mg. three times daily for three days was an adequate dose to increase bile secretion and intensify the liver and gallbladder shadow. In patients who had a marked pylorospasm the addition of an antispasmodic to each dose of the PTMC was followed by abolition of the spasm and improved tone of the pyloric sphincter. This was also noticeable in patients with spasm of the sphincter of Oddi. The doses as described above and used in our study (orally 75 mg. t.i.d. and parenterally 100 mg.) are considerably lower than those administered and reported on by the European observers (orally up to 250 mg. t.i.d. and parenterally 250 mg.). We found that the latter (especially intramuscular administration of 250 mg. or even 175 mg.) caused marked increase in the biliary flow, with discomfort, a feeling of fullness under the right ribs and at times marked cramps, requiring a mild sedative. However, when the dose

was reduced the results were less drastic and more gratifying. Combining the PTMC with an antispasmodic reduced the tendency of griping by relieving spasms.

Case Reports

The following nine case reports are representative for the 150 patients treated by us:

Case 1:—C. 4794—C. H., female, Para 2, age 28, weight 165¼ lbs., blood pressure 120/80.

Fig. 3—In this illustration the gallbladder and the stones are beautifully outlined. Previous attempts to visualize the gallbladder resulted in indistinct shadows. After several biliary drainings and the administrations of PTMC for 5 days and 6 capsules of Monophen previous to cholecystography, the above picture was obtained.

Complained of epigastric distress, belching, palpitation and shortness of breath, heartburn, gas pains. At times she is awakened at night; dull, drawing discomfort under right ribs.

Physical examination—gallbladder tenderness; confirmed by definite Murphy and Boas signs.

Fasting gastric analysis—Free HCl 30; total acids 43; occult blood negative; mucus plus; after stomach was lavaged the duodenal tube was introduced into the duodenum and large amounts of bile stained fluid was aspirated.

Microscopic examination showed 3 to 5 pus cells; columnar epithelium and bile salts.

Urine and stool nothing remarkable was found. C. B. C.—Hgb. 74 per cent; R. B. C. 4,610,000; W. B. C. 7,500; Polys 59 per cent; Lymphocytes 41 per cent and large mono 3 per cent. BMR 16 per cent plus.

Fluoroscopy and roentgenography—Gastrointestinal tract including barium enema failed to show any pathology. Cholecystography revealed a large atonic gallbladder which responded poorly to a fatty meal.

Patient was asked to return three days later for further study of the gallbladder content. A little difficulty was encountered this time in attempting to enter the duodenum, patient was given a hypodermic of Profenil and about 10 minutes later the first aspiration of bile was obtained. Injection of 30 c.c. of warm olive oil was given through the duodenal tube and the tube was clamped for 10 minutes. After removing the clamp, bile flow was established without difficulty. A. B. and C. bile was obtained and each specimen was examined routinely.

The following morning the patient went through the same procedure, requiring an injection of an antispasmodic in order to facilitate the introduction of the tube into the duodenum. Having accomplished the intubation satisfactorily, 25 mg. of PTMC in 10 c.c. of warm water was injected through the duodenal tube and washed down with an additional 10 c.c. of warm water. This was repeated at half-hour intervals until 75 mg. of the choleretic was given to the patient and the draining was continued for three hours. Each specimen was examined routinely.

After the above study the patient was given a gallbladder diet and PTMC, three tablets of 25 mg. each three times per day to be taken after meals, she also was advised to have her physician inject the antispasmodic 2 or 3 times weekly to overcome the spasm of the pylorus.

Continuing her tablets for two weeks, the patient lost most of her complaints especially the fullness under the right ribs, the belching was less and her bowels moved daily.

Mrs. C. H. was seen in the office February 8, 1952. She came in for a general checkup and was very happy that she lost all her previous symptoms which she complained of at the first visit. Re-xray of the gallbladder showed a smaller and more normal functioning gallbladder.

Case 2:—D. 1749, I. G., male, age 46, occupation, waiter, weight 233½ lbs., blood pressure 120/80. Mild colitis 23 years ago. Denied venereal diseases. Present complaint – pains on right side and under right shoulder blade. When pain occurs his skin turns greenish-yellow, has nausea, belching, heartburn and general abdominal discomfort. Rectal irritation especially marked after a bilious attack.

Physical examination – the liver is about two fingers below the right costal margin, smooth but tender, there is also definite tenderness in McBurney's and Boas' areas.

Fasting gastric analysis – Free HCl 24; total acids 41; occult blood negative; mucus 3 plus; bile plus; urine alkaline sp. gr. 1.010, otherwise negative. Stool (3 day meat free) – brown formed, acid, occult blood negative; mucus moderate; occasional vegetable fibres.

Blood count Hgb. 96 per cent; R. B. C. 4,910,000; W. B. C., 5,050; Polys 60 per cent; Lymphocytes 35 per cent; Eosin. 4 per cent; large mono. 1 per cent; platelets 210,000; Sedimentation rate normal. Blood sugar 108 mg. per 100 c.c.; cholestrol 209 mg. per 100 c.c.; Icterus index 12 units; Amylase 74 mg. per 100 c.c.; Lipase 1.5; Cephalin – flocculation 24 hour 1 plus; 48 hours 2 plus; Wassermann negative; BMR 5 per cent plus.

Fluoroscopy and x-ray examination of the gastrointestinal tract – marked hyperirritability and hypermotility; cholecystography showed an atonic and poorly emptying gallbladder.

This patient, too, went through the three tests, each one lasting 3 hours, the final with the PTMC tablets as a choleretic stimulant. Results were satisfactory. Patient was given a diet suitable for his condition, in addition he was instructed to take one 25 mg. PTMC tablet after each meal increasing the dose gradually until he was taking three tablets after each meal. He did not respond as readily as the previous patient because of his irregular hours and meals. In order to further test the efficacy of PTMC his physician was given several ampules and advised to give him 100 mg. by hypodermic and gradually increase the dose, watching for untoward symptoms. After the third injection (175 mg.) the patient was seized with violent cramps in the uper abdomen, nausea, retching followed by diarrhea. An antihistamine preparation was given to the patient and in less than one-half hour the symptoms subsided, leaving the entire abdomen sore and sensitive.

The patient was seen the following morning and the blood chemistry showed a marked change. The cholesterol and icterus index levels were elevated although there was no definite icteric tinge of the sclera or skin. The liver was more sensitive. These symptoms undoubtedly were brought about by the sudden increase in the biliary secretion and the sensitivity (allergic) of the patient.

Because of this episode the patient's diet was changed and a 25 mg. antihistamine tablet was given to him after each meal. In a week's time the patient's condition cleared up – the cholesterol and icterus index returned to their original level. Patient refused further treatment with PTMC.

This patient was undoubtedly allergic or sensitive to doses of PTMC larger than 75 mg.

Case 3:—B. 5239, E. S., female, Para 3, age 29, weight 158 lbs., blood pressure 120/70.

Chief complaint — pain on right side, no definite area. Gave birth to a baby 10 months previously.

Physical examination — slight tenderness over the gallbladder and appendiceal regions. The right kidney is also movable and tender. Rectal and vaginal examination negative. Patient refused to have further tests until she was relieved of her present complaints.

Preliminary treatment consisted of a selected diet avoiding fats, fried, cold and extreme hot food and drink. A quarter of a grain tablet of Luminal was prescribed three times daily. Fleets' phosphate soda, one teaspoonful and 15 drops of tincture of cardamon compound in a half glass of hot water was to be taken one-half hour before breakfast. The patient returned in ten days relieved of her distress.

She was advised that it would be necessary to have a thorough study made of her gastrointestinal tract including the gallbladder. A flat film of the gallbladder area failed to show the presence of calculi. Eight tablets of Priodax were given to her with instructions as to its ingestion. Next morning she presented herself for cholecystography and after the film was developed it failed to show the gallbladder. PTMC and Profenil tablets were given to her with six more Priodax. She was instructed to take one PTMC and one Profenil tablet after each meal for a period of three days and in the evening of the third day after dinner to take the Priodax tablets. The following morning the gallbladder was visualized showing the presence of two large calculi.

This same procedure was employed in several other patients and not only was the gallbladder visible but the liver was also more clearly outlined.

Case 4:—B. 2700, J. G., male, age 37, occupation, contractor and builder, weight 155½ lbs., blood pressure 110/65.

Chief complaint — bad taste in mouth, constipation, fullness in upper right quadrant of abdomen, radiating indefinite pains to back and at times under right shoulder blade and pain in the joints.

Physical examination — sallow look, tongue coated, breath — marked halitosis. Abdomen — no definite tenderness elicited. Rectal — external hemorrhoids.

Fasting gastric analysis — Free HCl 24; total acidity 40; occult blood negative — urine negative; stool — acid, foul, many undigested meat and vegetable fibres. Blood count normal — blood sugar normal — Cholesterol 340 mg. per 100 c.c. Uric acid 4.2 mg. per 100 c.c. Wassermann negative.

The routine duodenal intubation and three hour tests were carried out. After the administration of 75 mg. PTMC in the three half hour periods, the biliary content increased, a large amount of heavy syrupy (black) B bile was

obtained. PTMC tablets (75 mg.) three times daily were taken by the patient for a period of one week. On his return to the office, he claimed that the heaviness under his right costal margin had disappeared, there was no radiating pains and the odor of his breath was less pungent. He was again intubated and after obtaining bile-stained duodenal juice, 100 mg. of PTMC was injected hypodermically. Within 15 minutes there was a profuse flow of thick dark bile and for one and one-half hours continued to flow without abatement, gradually changing to lighter color.

This patient preferred the duodenal tube method and the injection of PTMC, rather than wait for the slower effect with the oral administration of the tablets.

After several drainings at intervals of two weeks, four weeks and two months, the symptoms complained of cleared up including the joint pains.

In previous articles published in the Annals of Internal Medicine, the senior author, in cooperation with Drs. Rawls and Collins reported their findings in relation to the liver, gallbladder and arthritis.

Case 5:–D. 2417, A. W., female, Para 2, age 25, weight 122½ lbs., blood pressure 120/80.

This patient had jaundice 4½ years while in a detention camp during World War II. She gave a very interesting history which dates back to about July 1951. While pregnant she developed jaundice and a temperature of 106°F. The treatment she received favorably influenced the course of the disease. Large doses of aureomycin brought her temperature down to normal, but her jaundice persisted until she miscarried at 6 weeks of pregnancy. X-ray examination failed to visualize her gallbladder.

Physical examination – Liver palpable and tender, the gallbladder area is also tender.

Fasting gastric analysis – Free HCl 10; total acidity 25; occult blood negative; mucus – large amount; bile 2 plus; urine – normal; stool occult blood negative, foul; mucus none; occasional vegetable fibres. Blood count – within normal limits.

After 6 capsules of Monophen the gallbladder was not visualized. She was given Choline and Inositol after meals and told to return in one month. Upon re-examination the liver and gallbladder tenderness had disappeared and she looked better and felt better.

Biliary drainage on successive days, the last one with PTMC 75 mg., gave good results. Examination of the aspirate showed no evidence of cholesterol or rock crystals. The patient was given 100 tablets of PTMC, 25 mg. each, to be taken at the rate of three tablets three times daily, totally 225 mg. per day, and a diet. Her recent office consultation, February 6, 1952, showed a healthy looking woman, who had practically no complaint except that she was always hungry.

She asked for more PTMC tablets, as she found that when she took them she felt well and had regular bowel movements.

Case 6:—D. 1562, J. L., male, age 62, weight 134 lbs., blood pressure 146/90.

His story was that he was told by physicians that he had a nervous stomach. He was unable to account for the constant loss of weight, unless it was due to the restricted diet. He also stated that while eating he had cramps in the stomach although there was no nausea or vomiting. At times he regurgitated his food as he ate it.

Physical examination – Liver is 3 finger breadths below the costal margin and extends over to the median line and left, it is smooth and only slightly tender on palpation. The spleen is barely palpable; right inguinal hernia, some hemorrhoidal tabs; the prostate is negative.

Fasting gastric analysis – Free HCl 5; total acidity 25; occult blood negative; mucus 2 plus; bile 2 plus. Urine negative. stool acid; occult blood negative; odor foul; meat fibres. Blood count: Hgb. 83 per cent; R. B. C. 4,150,000; W. B. C. 8,000; Polys 64 per cent; Lymphocytes 25 per cent; Eosin. 2 per cent; Large mono. 3 per cent. Sedimentation rate 6 mm. in 2 hours. Blood sugar 110 mg. per 100 c.c.; cholesterol 314 mg. per 100 c.c.; Icterus index 8.15 units; Amylase 122 mg. per 100 c.c.; Wassermann – negative.

Fluoroscopy and roentgenography of the gastrointestinal tract and the gallbladder – negative except for marked enlargement of the liver and slight enlargement of the spleen.

After the three three hour tests, the last with PTMC, the patient was given Choline and Inositol and a liver diet for two weeks. Upon his return PTMC tablets were given, gradually increasing the dose to 75 mg. three times daily.

Several months later the liver and spleen were not palpable and recheck of his cholesterol showed a marked decrease – 249 mg. per 100 c.c. as compared to 314 mg. per 100 c.c.

Patient was seen in the office February 6, 1952. He had gained weight, blood pressure was 140/85; the liver and spleen were within normal limits, he had no cramps, no regurgitation of food and his sallow look disappeared.

Case 7:—D. 1990, Wm. F. S., male, salesman, age 55, weight 177 lbs., blood pressure 100/70.

Chief complaint – belching, night and day, smokes heavily, no nausea or vomiting. Bowels are regular.

Physical examination – Throat congested, the liver is palpable three fingers below the right costal margin – rectal negative.

Refused gastric analysis – urine negative; stool foul, acid; moderate mucus; blood count – Hgb. 92 per cent; R. B. C. 4,490,000; W. B. C. 10,250; Polys 58

per cent; Lymphocytes 42 per cent. Sedimentation rate 6 mm. in one hour. Blood sugar 134 mg. per 100 c.c.; cholesterol 270 mg. per 100 c.c.; Icterus index 10 units; Amylase 36 mg. per 100 c.c.; Cephalin — flocculation 1 hour 2 plus; 48 hours 3 plus; prothrombin time 22 seconds; Wassermann — negative.

This patient was placed upon gradually increasing doses of PTMC until reaching three tablets of 25 mg. each three times daily (total daily dose 225 mg.). Within one month there was a definite improvement in the size of the liver and a recheck of the blood showed blood sugar 108 mg. per 100 c.c.; cholesterol 224 mg. per 100 c.c.; cephalin flocculation in 48 hours 1 plus.

Patient was continued on PTMC, Choline and Inositol and a liver diet for several more weeks with good results.

Case 8:—D. 389, F. S., female, age 58, weight 142½ lbs., Para 6, blood pressure 150/90.

Hysterectomy in 1935; gallstone operation 1941; in 1942 she was reoperated on for adhesions and obstruction of common duct (no calculi found in duct); at present is nauseous in addition has had about 10 to 15 attacks of pain in the past year; spells of weakness, very nervous, and has developed severe pain in the joints (arthritis).

Physical examination — arthritis, palpable mass at site of operation, large lipoma in mid back. Urine and stool negative. Blood count Hgb. 64 per cent; R. B. C. 3,730,000. Patient did not improve with diet and medication, became jaundiced, liver was large and tender, temperature 103-104°F, advised patient to enter hospital for observation and treatment. Condition became worse, operation revealed marked liver enlargement, adhesions, but no stones in the duct. A tube was introduced into the common duct and the patient made an uneventful recovery. After the operation and during the convalescence, to augment the flow of bile, PTMC was given in graduated doses up to 75 mg. three times daily without ill effects. The bile became less concentrated and flowed freely. In addition, the patient was given a capsule after meals of Thiamine HCl mg. 15; Ascorbic acid mg. 30; Choline dihydrogen citrate 0.5.

Recently the patient experienced some trouble and the bile flow became sluggish, the odor became marked and a severe dermatitis developed. PTMC plus the above capsules and tablets of chloresium were prescribed, the bile increased, the odor and dermatitis disappeared and the general condition of the patient improved.

Case 9:—C. 5696, H. M., female, married, Para 3. For several years had had upper abdominal discomfort especially after fatty meals. Constipated and at times has bitter taste in mouth.

Was first seen during an attack in the right upper quadrant, temperature 100°F, pulse 84, urine dark and frothy. Penicillin injections were given.

Physical examination – Rigidity of upper right abdomen, sensitive to palpation. Boas point was positive.

Treatment consisted of the usual measures to alleviate the acute phase. After three days, patient's symptoms abated and she was placed on a skim milk diet; penicillin injections were continued for another two days.

At the end of eight days biliary drainage and cholecystography was advised. At first patient was reluctant to permit passage of the duodenal tube but consented to cholecystography.

According to the patient's statement, previous attempts to visualize the gallbladder were unsuccessful. Keeping this in mind, Profenil and PTMC tablets were prescribed for three days preparatory to the administration of the gallbladder dye.

On the evening of the fourth day, a tablet of Priodax was given every five minutes for eight doses, and the patient was x-rayed the next afternoon.

Visualization of the gallbladder was unsatisfactory and no attempt was made to repeat the dose, but rather to attempt to drain the biliary tract and repeat the x-ray examination if and when bile was obtained through the duodenal tube.

After much coaxing the patient was persuaded to have the tube passed and to drain the duodenal content.

After the tube was in the duodenum an intramuscular injection of 1 c.c. of Profenil and 1 c.c. of PTMC (100 mg.) was given and five minutes later gentle aspiration was begun.

It took several minutes longer before results were noted. On aspiration a mucus plug was withdrawn and this was followed by a small quantity of viscid bile. Gradually more and more bile appeared including a thick tarry-like substance (static bile) which came through the tube with difficulty. Washing through the tube with warm normal saline, a clearer bile began to flow.

No attempt was made to continue the draining for a longer time. The tube was removed and the patient was given two PTMC tablets, 25 mg. each, three times daily after meals.

She was discharged from the hospital and instructed to continue her medication and diet for one week and to return to the office for duodenal draining.

On subsequent intubation after a slight delay, bile began to flow without added measures.

In order to make certain that the gallbladder would visualize, the PTMC tablets were increased to three after each meal, and Priodax (8 tablets) to be taken on the fifth day before cholecystography.

Results this time were satisfactory and the gallbladder was outlined without showing stones.

February 27, 1952 – patient had no attack, ate better, felt better and wished to continue PTMC tablets.

Summary and Conclusions

One hundred and fifty patients were studied over a period of almost two years without any untoward effect of PTMC when given in therapeutic doses (orally three tablets of 75 mg. per day and intramuscularly 100 mg.), except for only two patients who undoubtedly had an idiosyncrasy to all choleretics. Changes in the gastric analysis, blood picture and x-ray findings were favorable. PTMC has a definite choleretic action, at times more so than some of the other choleretics. It is absorbed quite readily and its action exerted within a period of two to three hours. There were no toxic manifestations although some patients complained of slight intestinal discomfort and occasional diarrhea. No impairment of the liver functions were observed during or after PTMC therapy. It has a salutary effect upon the biliary apparatus and many times the films taken in conjunction with Priodax or Monophen showed a much clearer liver and gallbladder shadow due to the active choleretic action of the PTMC.

Like other choleretics, PTMC should not be used in the presence of acute biliary conditions, in common duct obstructions, hepatitis or marked cholangitis; it should be avoided when marked cicatrication or organic narrowing of the duct is suspected.

It may be safely used in functional disturbance of the liver, in biliary dyspepsia, chronic cholecystitis, nonobstructive cholangitis, biliary dyskinesia, biliary stasis, pre- and postoperative conditions where the bile flow is sluggish. PTMC compares favorably with other choleretics in use for many years.

PHYSIOLOGIC BASIS FOR THE THERAPEUTIC EFFECTS OF CORTISONE*†

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Cortisone and ACTH (which stimulates the patient's own adrenal cortex to secrete the C_{11} oxysteroids) are known to be therapeutically effective in such diverse conditions as the so-called collagen diseases, including rheumatoid arthritis, acute rheumatic fever and lupus erythematosus; hypersensitivities, including bronchial asthma, hay fever, drug sensitivities and urticaria; and acute inflammatory diseases of the eye, skin and other tissues. The fact that these "miracle drugs" do not cure any disease which is not self-limiting in nature, is beside the point for this particular discussion. The fact remains that, during treatment with these agents, we can bring under control diseases against which we were formerly relatively helpless. It therefore behooves us to try to understand the mechanism of action of these drugs, both from the standpoint of learning what

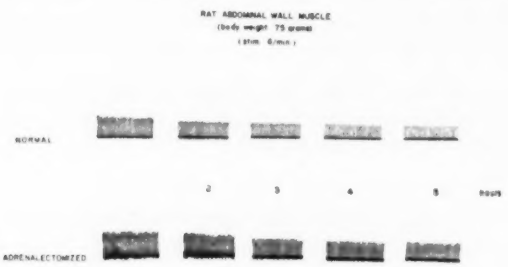

Fig. 1

the various diseases which yield to them have in common, and with the view to achieving better use of these drugs or of other drugs which might have the same action.

It is a striking fact that in none of the diseases which are controlled by these drugs, (except Addison's disease in the case of Cortisone) is there any evidence of a consistently subnormal functional state of the adrenal cortex or of

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a deficiency of the C_{11} oxysteroids. Hence, we must assume that the therapeutic benefit results from a greater than normal concentration of the C_{11} oxysteroids in contact with the diseased tissues, perhaps because they need more than the normal amount, or because they utilize or destroy more than the normal amount. It is evident that the action of Cortisone is a direct and local one on the diseased tissue, because striking therapeutic effects can be obtained in inflammatory diseases of the eye or skin by the local application of such minute amounts of the drug as would have no perceptible influence on the whole organism, even if they were entirely absorbed into the general system.

Because the administration of adequate doses of Cortisone to normal laboratory animals or man, causes important changes in protein, fat, carbohydrate and mineral metabolism (Table I), it is tempting to assume that the various diseases controlled by Cortisone have some metabolic defect in common, and that the drug corrects this defect. These indices of metabolic function, however, are not usually found to be abnormal in the diseases controlled by Cortisone;

TABLE I

METABOLIC EFFECTS OF CORTISONE

Increases		Decreases
Protein Catabolism		Growth
Fat Mobilization		Carbohydrate Tolerance
Potassium	Excretion	Insulin Sensitivity
Phosphate		Sodium Excretion
Urate		17 – Ketosteroid Excretion
C_{11} – Steroid		

the therapeutic effects of Cortisone administration are not paralleled by changes in these indices; and the re-appearance of signs and symptoms after discontinuation of therapy cannot be correlated with the subsidence of the metabolic changes induced by Cortisone.

From the beginning of its work, our group was impressed by the rapidity with which definite improvement in signs and symptoms may follow the therapeutic administration of Cortisone. For example, in rheumatoid arthritis the pain and stiffness in joints may be partially (but dramatically) relieved within a few hours after the first dose of Cortisone, long before any metabolic effects can be demonstrated or expected. This time sequence seems more characteristic of a neurocirculatory effect than of a metabolic effect, and is reminiscent of a similar observation regarding the effects of adrenal cortical extract on the signs and symptoms of Addisonian crisis. The intravenous administration of aqueous adrenal cortical extract to a patient in crisis raises the blood pressure and relieves the extreme weakness and gastrointestinal symptoms long before there are any measurable changes in the electrolytes, the nonprotein nitrogen, or the sugar of

the blood. It therefore appeared reasonable to us that, rather than to plunge into an attempt to fathom the mechanism of action of Cortisone on various diseases of unknown etiology, it would be more feasible to start by analyzing in detail the effects of Cortisone on the adrenalectomized animal under stress.

We chose muscular exercise as the most suitable and convenient stress for our work, because it can be used quantitatively, and because it can be applied to isolated muscle *in vitro* as well as to the whole living organism. It had been shown previously, by Ingle and others, that adrenalectomized animals maintained in excellent clinical condition on desoxycorticosterone acetate (DOCA) fatigue very rapidly when subjected to continuous muscular exertion, such as swimming or repeated electrical stimulation of certain muscle groups. The muscular contractions rapidly diminish in force and then cease, despite continued stimulation. If the stimulation is persisted in, the animal goes into "shock" and soon dies. It occurred to us that if the easy fatigability of the adrenalectomized

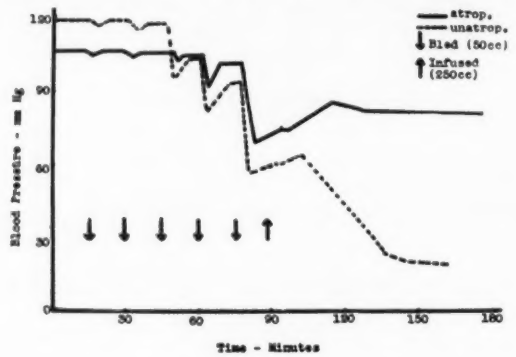

Fig. 2

animal were due to a metabolic defect in the muscle, it should be possible to compare the contractile powers of isolated muscles from normal and adrenalectomized animals respectively, by working them *in vitro* under conditions in which no other variable in the body could influence the comparison. Accordingly, suitable thin muscle strips (abdominal muscle and diaphragm) were removed from normal and from adrenalectomized rats and were suspended in an oxygenated buffered medium. These muscles were then stimulated electrically to contract at regular intervals, and the contractions were registered on a kymograph. Some of the muscles were stimulated directly, and some (diaphragm) were stimulated through the attached motor nerve. Figure 1 is typical of the results of many such experiments. Isolated muscle and isolated nerve-muscle preparations of the adrenalectomized animal were capable of just as much work as muscles from normal animals, under the same experimental conditions. Hence, the fatigability of muscle in the adrenalectomized animal *in vivo* could not be attributed to any intrinsic disturbance in the nerve, the myoneural junction, or the muscle fibre.

These observations and conclusions naturally directed attention to the possibility that the failure of a neurocirculatory mechanism might be responsible for the easy fatigability and early collapse of the working adrenalectomized animal. In the normal animal, exercise of a muscle group evokes a widening of the capillary bed and increased bloodflow through the working parts; while at the same time there is a compensatory decrease in the vascular bed elsewhere, particularly in the viscera. The failure of this neurocirculatory adjustment in the adrenalectomized animal, could cause a drop in blood pressure, with consequent decreased bloodflow through, and fatigue of, working muscles.

To test this hypothesis, mean arterial blood pressure and the work capacity of muscles were observed simultaneously in normal dogs and in DOCA-treated adrenalectomized dogs, respectively. The animals were anesthetized and the gastrocnemius-soleus group of muscles of one hind leg was repeatedly contracted by electrical stimulation. A suitable weight suspended from the severed and exteriorized Achilles tendon, determined the work performed at each con-

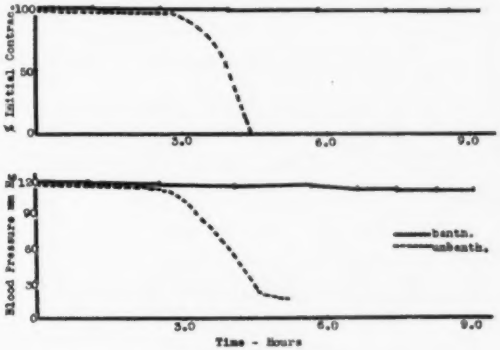

Fig. 3

traction, and was connected to a recording kymograph. In the normal animals, no muscular fatigue was demonstrable even after six to twelve hours of continuous contraction. In the adrenalectomized animals, fatigue set in within one to three hours from the beginning of stimulation. Figure 2 represents a typical experiment in an adrenalectomized animal, and shows that a marked fall in blood pressure precedes muscle fatigue. Furthermore, the administration of a vasoconstrictor substance (noradrenalin) which causes a temporary restoration of the blood pressure level, results in a correspondingly temporary restoration of muscle response to the electrical stimulation. Table II gives the actual time sequences in a few experiments. It may be seen that the fall in blood pressure always preceded the onset of fatigue by a considerable interval; and that once fatigue did set in, death was not far behind. Analyses of arterial and venous blood pressure records indicated that the onset and degree of fatigue depended upon the height of the mean arterial blood pressure, below a critical level of about 70 mm. Hg.

The heart rate did not change significantly; neither did the venous pressure It was therefore concluded that the muscular fatigue of the adrenalectomized animal is secondary to the development of vascular incompetence; and that the latter is chiefly a reflection on peripheral circulatory failure, rather than of cardiac failure.

Further work with noradrenalin was undertaken, to gain more insight into the functional relationship between the C_{11} oxysteroids of the adrenal cortex and the neurocirculatory mechanism. Noradrenalin was chosen because of recent experimental evidence that it is most probably the normal physiologic vasoconstrictor substance liberated at the nerve endings of the adrenergic system. Figure 3 represents one such experiment, in which a single dose of noradrenalin was administered at repeated intervals to normal and adrenalectomized animals respectively. It will be noted that the normal animal maintained his mean arterial blood pressure (white blocks) throughout the period of observation, and that

TABLE II

Condition of Animal	Time From Beginning of Stimulation To:		
	Onset of B.P. Fall	Onset of Fatigue	Death
1. Adrenalectomized	48 mins.	65 mins.	79 mins.
2. "	280 "	290 "	300 "
3. "	235 "	280 "	330 "
1. Normal	Blood pressure maintained until sacrificed.		
2. "	No fatigue manifested.		(6 and 12 hours)

each time the noradrenalin was given it caused about the same increase in blood pressure (black blocks). In sharp contrast to this, the adrenalectomized animal gave a smaller response each time the noradrenalin was administered. Furthermore, the very giving of the noradrenalin seemed to have a deleterious effect on the blood pressure of the adrenalectomized animal, so that it was approaching shock levels by the end of the experiment. Figure 4 represents a similar experiment, except that the noradrenalin was administered by continuous infusion. I should like to direct your attention particularly to the third hour of the experiment, at which time the intravenous injection of aqueous adrenal cortical extract in the adrenalectomized animal caused temporary, but very pronounced increases in blood pressure, even though the pressure had been falling in the face of a continuous infusion of a large amount of noradrenalin. The same doses of adrenal cortical extract had no effect whatever in the normal animal. It therefore appeared that the adrenalectomized animal under stress cannot properly

re-distribute blood because of the relative ineffectiveness of noradrenalin in reflex vasoconstriction. The C_{11} oxysteroids seemed to be necessary for the proper degree of vascular response, even though these substances are themselves ineffective as vasoconstrictors.

These observations and conclusions were confirmed in an entirely different way, using the Chambers-Zweifach mesoappendix preparation in rats. This method permits an intimate study of the responses of the splanchnic bed to various pharmacologic agents, by direct microscopic observation. The method consists of exteriorizing the portion of the gut containing the mesoappendix and placing this little mesenteric fold in position for microscopic observation. The field is irrigated by a continuous flow of a warm Ringer's solution containing gelatin. Under these conditions observation can be made of the state of the vessels, the speed of blood flow, damage to vessel walls, hemorrhage, and other changes. It is, of course, easily possible to observe the reaction of such a vascular bed to drugs given parenterally or applied topically.

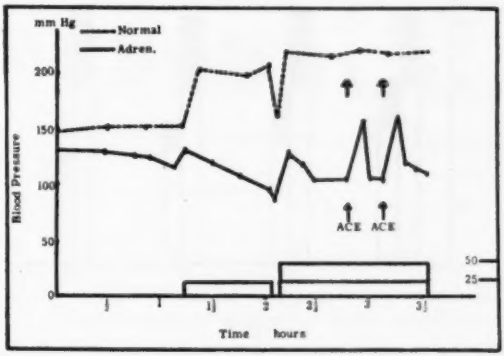

Fig. 4

In the normal rat there occurs the phenomenon called vasomotion, which consists of alternate constriction and relaxation of the arterioles and metarterioles. When 0.02 c.c. of a 1:800,000 solution of noradrenalin is applied topically, there is a very sharp vasoconstrictor response, with momentary stoppage of flow, and an equally brisk recovery to the initial state. Such an application can be repeated every ten or twenty minutes for hours with equivalent results. That is, the sensitivity of the normal blood vessels to this drug remains the same even after hours of exposure of the normal mesoappendix. A parenteral injection of 0.3 c.c. of 1:1000 noradrenalin causes prolonged constriction. Complete recovery occurs, however, and no residual change can be seen in the field of observation.

The adrenalectomized DOCA-treated rat in good clinical condition, maintaining a normal electrolyte balance, behaves in an entirely different manner. The initial sensitivity to noradrenalin is like that of the normal, but with time there is an increasing resistance to the drug, so that after one or two hours

of observation, from ten to fifteen times the initial effective dose is necessary to produce local constrictive effects. Obviously, the experimental procedure itself represents a "stress", and the behavior toward noradrenalin is analogous to the course of events in the adrenalectomized dog under the stress of muscular exercise. A large parenteral dose of noradrenalin will produce constriction but the recovery phase is poor and diapedesis and hemorrhage can be seen to occur. The topical application of small amounts of adrenal cortical extract (but not of DOC – glucoside) restores the sensitivity to topical noradrenalin within 15 or 20 minutes. The effect of the adrenal steroids is local, and these steroids by themselves do not have any vasoconstrictor action. Obviously, therefore, the C_{11} oxysteroids have to be present for the effector portions of the small vessels to be able to respond to noradrenalin. (The immediate response of the vessels of the mesoappendix to the vasodilating effect of acetylcholine and histamine does not seem to be altered by the absence of C_{11} oxysteroids).

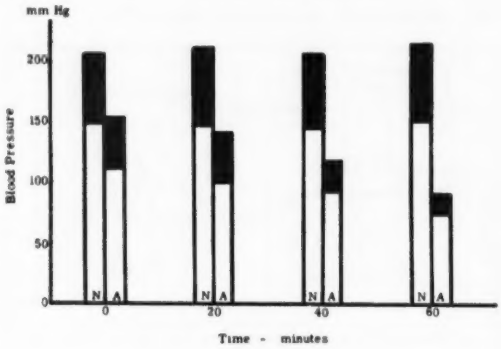

Fig. 5

In succeeding experiments a more acute stress situation was produced by the subcutaneous injection of 0.3 c.c. of a 4 per cent formalin fixative solution. Within 15 or 20 minutes intense activity could be observed in the mesoappendix preparation: vasoconstriction, cessation of blood flow, localized dilatations of arterioles and venules, diapedesis, and hemorrhage. Death occurred approximately one hour after the administration of formalin. The control group of normal animals showed no vascular reaction whatever to this dosage of formalin and all survived. Because the vascular picture produced in the formalin experiments was similar to the reaction seen in the adrenalectomized rat given a large parenteral dose of noradrenalin, it was postulated that the formalin effect was mediated by the secretion of sufficient noradrenalin to produce constriction but with poor recovery. Accordingly, dibenamine was administered to adrenalectomized rats prior to the formalin stress. Dibenamine completely prevented the vascular damage that otherwise followed formalin injection. Dibenamine also prolonged the survival time of adrenalectomized rats in which stress was produced by formalin administration.

This favorable effect of an autonomic inhibitor opened up new vistas as regards experimental approach, and as regards possibilities for clinical application. We therefore returned to the whole animal, to study the influence of other autonomic inhibitors. Figure 5 represents an experiment in which the gastrocnemius-soleus group of muscles was exercised in anesthetized adrenalectomized dogs, as previously described. None of the animals were given any Cortisone or adrenal cortical extract, but two of them were kept under the influence of banthine from the beginning of the experiment. It will be noted that while the untreated animals exhibited the usual drop of blood pressure in about three hours, followed by the usual failure in muscular contraction, the banthinized animals maintained their blood pressure and their ability to work for the nine hours that the observations were continued. Figure 6 shows a similar experiment, but using a different stress and a different autonomic inhibitor. Here, one group of anesthetized adrenalectomized dogs was repeatedly bled until the blood pressure fell to shock levels, at which time all the blood which had been taken out was

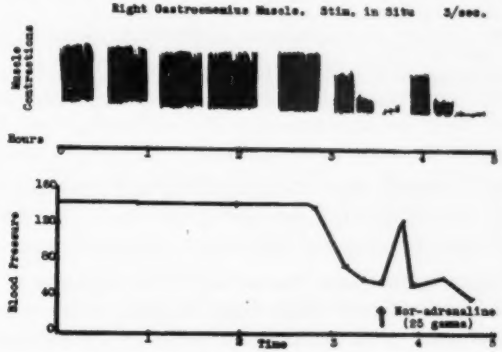

Fig. 6

re-infused. In the untreated animals the re-infusion of the blood had only a slight and temporary effect on the blood pressure, which continued to fall rapidly to the death of the animals. In the dogs kept under the influence of atropine the re-infusion of the blood caused a better return of the blood pressure level, but, what is more important, the restored level of blood pressure was maintained and the animals lived.

It is much too early to say how much of the therapeutic effects of Cortisone are explained by its participation in this neurocirculatory mechanism. It would certainly appear that its dramatic anti-inflammatory influence might well be accounted for in this way. But whether this is the only mechanism, and what (if any) is its relationship to the various metabolic effects of Cortisone, we have as yet no inkling. Nor can we yet estimate the possible practical clinical uses of the autonomic inhibitors, with or without Cortisone, in the diseases we have been discussing. However, at least a beginning has been made towards understanding the important and difficult problem of the mechanism of action of Cortisone.

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Discussion

Dr. I. Snapper:—Hardly any experimentation had preceded the introduction of Cortisone and ACTH into the practice of medicine. No wonder that these drugs are less effective than the first enthusiastic publications seemed to indicate.

It is very gratifying that now, thanks to the investigation of Dr. Soskin and his group, the actual action of these drugs is being analyzed experimentally. Ultimately, in ten years' time perhaps, we will have a rational basis for the clinical application of these drugs.

Dr. Soskin said that the rapid action of Cortisone within a few hours upon symptoms and signs of disease, indicates more circulatory than metabolic effects. However, the increase of uric acid excretion in humans takes place within four hours after the injection of Cortisone.

In Dr. Soskin's dogs the blood pressure goes down before fatigue sets in. Here the heart shadow should decrease in size just as is the case in members of rowing crews who collapse after they reach the finish. The latter phenomenon is also neurocirculatory in origin.

Dr. Samuel Soskin:—There is little I can add. Dr. Snapper is, of course, right. Uric acid can be excreted within four hours; but the point I tried to bring out was that the dramatic improvement in signs and symptoms seemed out of proportion to any metabolic changes that were observed.

So far as the heart is concerned, again I think Dr. Snapper is probably right. We did not, however, make any such observation, so I cannot confirm it.

INTESTINAL STRANGULATION OBSTRUCTION*

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Strangulation obstruction of the intestine is an intriguing lesion from both the clinical and experimental points of view. Clinically it stands as a diagnostic challenge in every case of intestinal obstruction. Experimentally it remains after 50 years of intensive investigation, an enigma for those who have sought to explain how it causes death. Nonetheless a great deal has been learned from careful, relentless clinical and laboratory studies, so that today the mortality following strangulation obstruction is no higher than that of other lesions responsible for the acute abdomen.

In this discussion I wish to present some of the most recent experimental work on the subject and to touch on the clinical application of this work.

By way of definition it can be stated that when intestinal obstruction from any cause is complicated by impairment of blood supply to the involved loop, the term strangulation obstruction is justified. The most common cause is the so-called external strangulated hernia. Less common but more difficult to diagnose are the internal strangulated herniae caused by bands of adhesion or by peritoneal fossae. Strangulation is also a complication of intussusception, torsion, volvulus or any other closed loop lesion.

Recently Dr. Jordan Daniels and I[9] studied 100 consecutive cases of strangulated hernia at Michael Reese Hospital and found that the ages varied from the earliest hours of life to over 80 years. Males constituted 64 per cent of the sample and females 36 per cent. The proportion of existing herniae which become strangulated is not known exactly. However, of the total number of herniae admitted for surgery, we found that about 8 per cent of such admissions are for incarcerated or strangulated herniae.

From the standpoint of morbid physiology a strangulation consists of the triad: simple obstruction above the involved area; closed loop obstruction of the involved segment; and interference with blood supply of the involved loop.

It is obvious, then, that the lesion is a complicated one and results in all the consequences pursuant to intestinal obstruction in addition to those of death of tissue, either impending or actual. Furthermore, the local factors involved in the mechanical derangement are reflected in the general physiological upset which in turn gives rise to symptoms varying from mild to profound.

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*Presented before the Course in Postgraduate Gastroenterology of the National Gastroenterological Association, Chicago, Ill., 20, 21, 22 September 1951.

From the Departments of Surgery, Northwestern University Medical School and Michael Reese Hospital, Chicago, Ill.

The usual type of strangulation is one in which the veins to the segment are occluded first. This has been designated "venous strangulation". The local changes following venous strangulation are venous engorgement, hemorrhagic infiltration of tissue, spasm of arteries, thrombosis of vessels and actual necrosis of tissue. Necrosis of mucosa occurs first and may result in sloughs of considerable size. Distention of the involved loop may be only moderate, and contrary to popular thought, is not an important factor in the question as to whether or not the loop will perforate except in very short segments. Perforation of a loop is more dependent upon the interplay between vascular impairment and bacterial invasion. The further down in the gastrointestinal tract the strangulation occurs the more distensible is the bowel wall. Upon release of a strangulation, mucosal sloughs may eventually be completely restored due to the remarkable regenerative power of the mucosa. If destruction is severe enough, healing by scar tissue takes place. The greater the blood extravasation into the tissues of the intestinal wall the more severe is the fibrous thickening upon recovery. This thickening occurs mainly in the submucosal layer.

Short loop strangulations including Richter's type* are more prone to be complicated by rapid death of tissue and perforation than are longer loop strangulations. Very long loop strangulations are more apt to result in a remarkable fluid and blood loss and may lead to shock and even death of the patient before irreversible changes have occurred in the involved loop. In contrast to these two types, the type of strangulation which has attracted the attention of investigators for many years has been the so-called medium length loop, low intestinal strangulation in which neither perforation nor remarkable fluid loss can account for the severity of the general symptoms. It is in this type of lesion that a "toxic factor" has been sought.

The fundamental phenomena ultimately responsible for most local and general disturbances arising in the involved loop are (1) interference with circulation and (2) bacterial invasion. Superimposed upon these are the consequences of simple intestinal obstruction above the strangulated loop, which will vary in accordance with whether the lesion is high or low in the gastrointestinal tract.

Vascular Factor

My associates and I[12] have shown that the vascular responses in the vessels of a strangulated segment of intestine are much the same as those in other areas of the body, such as the lower extremity for example, following vascular occlusions. Following the usual type of venous strangulation in which the veins are primarily occluded, the involved loop soon assumes a deep purple color. Arterial pulsations carry on for a while, then diminish remarkably and finally cease. Microscopic observations have shown that there is a marked arteriospasm ac-

*Richter's hernia is one in which a nipple of gut wall is caught in a hernial opening, without occluding the lumen of the gut.

companying such a venous occlusion. The result, then, on the involved loop is not only one of venous engorgement, but an actual diminution of arterial oxygenated blood to the segment. Intravascular erythrocyte agglutination (so-called sludge) forms in both the arteries and veins as a result of the stagnant anoxia. When the sludged masses become attached to the endothelial walls of the small vessels, soft thrombi occur[11]. Thrombosis following vascular occlusion occurs first in the smallest radicals and later in the larger vessels.

When a short segment of bowel is involved bacterial invasion readily occurs in the hemorrhagic and anoxic tissue. Death of tissue occurs more rapidly, therefore, in short loop strangulations where the added factor of distention and resultant vascular compression is proportionately greater.

Initially, there is a transudate of a readily coagulable plasma-like fluid which later becomes blood tinged[13]. As the occlusion persists transudation from the bowel wall into the peritoneum becomes darker in color and less coagulable, the latter due to the anticoagulant effect of streptokinase[1]. Streptokinase permeates through the bowel wall into the abdominal transudate as a result of bacterial action within the intestinal lumen and bowel wall.

Upon release of a strangulation there is a significant period in which residual spasm persists in the arteries of the segment. Consequently there is a lag period before the veins are able to diminish their engorgement, provided the vessels still retain reactivity. Diminution of venous engorgement under such circumstances is directly proportional to the rate of arterial blood flow through the accompanying arteries as well as to the state of fluidity of the blood within the vessels. Resuscitative measures at the operating table, therefore, are aimed primarily at releasing residual vasospasm and at improving the rate of circulation of the loop. Tests for viability are primarily based upon the success of resuscitative measures in reestablishing circulation.

Bacterial Factor

The remarkable protective effect of antibiotic and chemotherapeutic agents in intestinal strangulation obstruction has served to revive the importance of the bacterial factor. The work of Sarnoff and Poth[19], Harper and Blain[6], Lockwood and associates[17] and others[2, 4, 8] provides ample evidence in favor of the importance of eradicating the effects of bacteria in strangulation. These studies have served to substantiate the almost forgotten work of Murphy and Brooks in 1915[18] and that of Dragstedt and co-workers in 1917[5], who presented evidence that the origin of the toxicity in closed loop obstruction is bacterial in origin. Recently my associates and I at Northwestern University Medical School were able to show rather conclusively that sterile devascularized intestine within the peritoneal cavity undergoes autolysis with no adverse effects on the host[14].

Yet modification of the bacterial factor in strangulation has definite limitations. In another experiment[8] we strangulated loops of ileum in dogs long enough

before release to result in death of 100 per cent of the control series. In a series of comparable dogs treated with massive doses of penicillin, upon release of the strangulation all animals survived, but certain complications ensued. The limitations on the use of antibiotics are based upon the fact that the greater the destruction of the tissues the longer is the pathway to recovery. We were able to demonstrate disturbances in the peristaltic gradient, stenosis of the involved loop, constriction rings at the site of the occlusive bands, plastic adhesive peritonitis and intussusception.

Although there is a stage in the process of hemorrhagic infarction pursuant to strangulation during which the bowel no longer responds to resuscitative measures and is, therefore, considered nonviable, the cells of the mural structures need not have undergone irreversible damage. Beyond this stage antibiotics cannot be expected to be of predictable value. Penicillin will not revive gangrenous tissue. Therefore, since it is almost impossible to delineate the end stages of reversibility from frank infarction it is more advisable to resect such a segment than to depend upon the antibiotics.

The bacterial and circulatory factors are interdependent. When antibiotics are used they reach the intestinal tissue by diminished blood supply, but are able under certain circumstances to limit bacterial invasion sufficiently to interrupt the process of destruction and maintain anatomical integrity of the intestinal wall until adequate blood supply can be obtained to promote healnig.

Toxic Factor

The invasion of damaged tissue by bacteria appears to be the initiating cause of a toxicity, the nature of which has been the source of a great deal of investigation for many years. Many substances such as histamine[20], nucleoproteins[7], ptomaines[3] and a long list of others have been purported to play a part in the toxicity. Recent advances in enzyme chemistry have allowed the identification of certain bacterial enzymes upon which chemical and immunological studies can be made. All these studies were stimulated by the fact that although the source for the toxemia lies largely in the virulence of the invading bacteria, the result on the host is not a bacteremia and it is known that a substrate of damaged tissue is necessary in order for the toxicity to progress. Recently Tanturi and associates[21] in our laboratory have identified lecithinase, hyaluronidase and streptokinase in the peritoneal fluid of dogs with strangulated gangrenous appendicitis. They have also shown that in strangulated obstruction, a lecithinase, probably identical with alpha toxin of type A. Cl. welchii was demonstrable in significant amounts in the lumen of the strangulated loop and in the peritoneal fluid. In the absence of perforation hyaluronidase was not detectable in the peritoneal fluid. After Dr. Tanturi returned to his native Argentina, my associates and I continued work with lecithinase and found that lecithinase in significant amounts is recoverable in the thoracic duct lymph of dogs with strangulation obstruction[15]. We also performed experiments in which we infused normal

dogs' blood with commercial preparations of the alpha toxin and found that it produced the same ill-effects as we found in our strangulated animals. Without delving too deeply into the work along these lines, I should like to relate some of our confirmatory work identifying lecithinase as one of the toxins of some importance in strangulation obstruction. For example, serum very high in antilecithinase can be manufactured in an animal which has been subjected to an almost fatal strangulation. If the segment is resected and the animal is allowed to remain alive for about 6 weeks the animal will develop a limited "immunity" to strangulation obstruction. That is to say, if a second strangulation is then made, the animal's longevity will be from two to three times that of a control dog. Furthermore, the convalescent serum from such an animal will actually neutralize the lecithinase obtained from the loop or peritoneal cavity of another animal with strangulation obstruction.

I wish to emphasize that there are undoubtedly other toxins which play a role in the total picture. Very recently Light[16] presented evidence to indicate that lysozyme is one of the toxins present in closed loop intestinal obstruction. As newer phases of enzyme chemistry develop I am sure that still other enzymes will be identified since enzymes have a habit of playing in teams rather than individually.

It should further be emphasized that the total toxicity of a patient with strangulation obstruction is the result of many things, including fluid and electrolyte imbalance which must be corrected as a part of therapy.

The loss of fluids in relatively short loop strangulations has been shown recently to be less a factor in the general toxic state than was previously thought. However, in long loop strangulation there may be sufficient fluid loss to cause shock, without the need for toxic factors as a contribution to the shock state. In such an instance the patient may be in extreme shock while the involved loop is still viable and not particularly invaded by bacteria. We consider the contribution to the general morbid picture by neurogenic factors a minor one. With sudden distention, which usually does not occur in strangulation obstruction, there may be stimulation of sympathetic nerve endings in the bowel which give rise to a state of primary shock. As this passes away a more critical and more profound secondary shock state may supervene.

Slow Versus Rapid Strangulation

Thus far we have considered the interplay between the vascular factor and the bacterial factor in the production of a toxic state. We have also considered the question of the length of the loop in the resultant clinical picture. One other factor remains to be discussed which was the subject of a recent experimental study by our group[10]. It involves the question of slow versus rapid strangulation.

By placing loosely constricting tapes about the intestine in dogs we were able to reproduce the picture of incarceration without strangulation. We found

that if a loop of bowel had been incarcerated for some length of time, sudden strangulation of such an incarcerated loop will result in death of the loop considerably more rapidly than when a freshly strangulated segment is not preceded by incarceration. During the period of incarceration there is an elevation in the serum antilecithinase titer. However, this is a moderate elevation and is not sufficient to protect the animal when the strangulation supervenes. Furthermore, during incarceration several processes occur in the involved loop. Initially there is edema of the incarcerated mesentery and bowel. We found that bacteria invade the lining cells of the dilated lymph channels very early. Later there develops an hypertrophy of all muscular layers in the loop and an excess of fibrous tissue is laid down in both the mesentery and intestinal tissue. When sudden occlusion supervenes, the tissue is less resistant to the sudden anoxia than is normal tissue. In one series of animals in which sudden strangulation was allowed to occur spontaneously after incarceration, it happened at such irregular times that we found we could not predict its occurrence.

These studies emphasized two important clinical features to us: (1) incarcerated herniae whether they are symptomatic or not, demand surgery at an early stage; (2) when viable bowel is found upon freeing an incarcerated nonstrangulated hernia, antibiotics are in order because of the early invasion of the mural structures by bacteria.

Clinical Studies

Our clinical studies referred to earlier in this discussion[9], emphasized that at the present time the unavoidable mortality for intestinal strangulation obstruction is in the neighborhood of 6 per cent. Factors which we found significant in the mortality were the existence of concomitant diseases involving the heart, liver, or kidneys, the duration of the strangulation prior to surgery, length of the involved segment, nature of the peritoneal transudate and the type of surgical treatment which embodies the possibility of errors in judgment of viability at the operating table.

It must be mentioned that treatment and diagnosis run hand in hand in the differentiation between simple and strangulating obstruction. Intestinal intubation, by means of a Miller-Abbott or similar tube or Wangensteen suction with a Levin tube in the stomach, is a very important procedure both diagnostically and therapeutically. The administration of intravenous fluids to restore fluid and electrolyte balance is of utmost importance in the management. Whether surgery is to be performed or not, these two procedures are mandatory. The warning must again be made, as it has been made many times in the past, that the too protracted use of intestinal suction may allow an intestinal strangulation to become infarcted. We have used as a criterion in borderline cases a dictum which has been used by many other surgeons; if a patient with intestinal obstruction of unknown etiology has not improved appreciably after 24 hours of good management, operation should be performed. When an external hernia is not obvious

to the examiner in the presence of obstructive symptoms, the problem of differentiation between strangulation and simple obstruction becomes essential. In addition, it is important to rule out other types of pathology responsible for the so-called acute abdomen which might simulate the symptoms of strangulation obstruction.

During palliative management the differentiation between simple and strangulating obstructions must be made. The presence of signs of irritability of the parietal peritoneum may be sufficient to clinch the diagnosis. We have found it advantageous to apply a few simple criteria in the differentiation. A flat x-ray plate of the abdomen may be helpful if it shows a dilated loop persistently present in the same part of the abdomen rather than the step-ladder appearance of simple obstruction. It is particularly important to note whether the mucosal markings in this dilated loop are present or absent. In the presence of strangulated obstruction these are almost always absent. The persistence of pain between cramps has been a rather reliable sign pathognomonic of strangulation, in contrast to the disappearance of pain between cramps in simple obstruction. In simple obstruction the distended abdomen is not particularly painful when cramps are not present. The patient with strangulation obstruction, on the other hand, is almost never free of pain. When abdominal tenderness supervenes on signs of simple obstruction, the examiner should suspect strangulation. Occasionally a mass can be palpated either through the abdominal wall or by rectal or vaginal examination.

If I may, I should like to repeat Wangensteen's statement[22] that there is less harm in operating upon an abdomen containing distended bowel without strangulation than there is in procrastinating too much by decompressing the distended bowel proximal to a strangulation.

Occasionally simple obstruction of the colon may produce signs which are quite similar to those of intestinal strangulation. This is due to the fact that a marked increase in intraluminal pressure in the colon can occur in the presence of a normally functioning ileocecal valve, thus producing a closed loop obstruction.

We feel that it is important to perform a serum amylase test early in the course of all acute abdominal conditions in which the diagnosis is questionable. Only too often the reflex distention of a loop of bowel as seen in the x-ray gives the examiner the notion that he is dealing with a case of strangulation obstruction, whereas actually this is a common accompaniment of acute pancreatitis. The diagnosis of pancreatitis can be made quite simply early in its course by finding a markedly elevated serum amylase.

Time does not allow for a full discussion of the operative treatment including tests for viability, nor a discussion of surgical methods of resection and anastomosis. Suffice it to say that when the least iota of doubt exists regarding the viability of a released loop of strangulated intestine, resection and primary anas-

tomosis should be done. Furthermore resection and primary anastomosis have come to replace exteriorization in the treatment of devitalized bowel in all types of strangulation obstruction by the most competent surgeons.

The widely quoted high mortality rates of the past are still being used today and exert an unfortunate influence in the distortion of the surgical approach to the problem in one of several ways. (1) The tendency to expect a high mortality rate might falsely justify a death; (2) resection, conceivably a life-saving measure, might be postponed or allayed in a futile and time-consuming effort to revive dead bowel; and (3) the tendency to replace bowel of questionable viability might exist in the hope that the low mortality rates in this maneuver will mysteriously protect the patient.

In our recent clinical study which carried an overall mortality of 12 per cent, one-half the deaths were considered avoidable in terms of present day knowledge. The important therapeutic points as we see them are as follows: (1) elective surgical repair of all uncomplicated herniae; (2) the emergency surgical intervention for all complicated external herniae as soon as the condition of the patient permits; (3) judicious employment of adequate supportive care such as suction, parenteral fluid and electrolyte therapy and antibiotic therapy in all cases; (4) the adequate use of blood and plasma when indicated; (5) attention to the dangers of the too protracted use of suction in the presence of mechanical obstruction with continued abdominal pain; (6) resection and primary anastomosis when resuscitative measures leave any doubt regarding the viability of a released loop; (7) careful examination of the thinned-out portions of bowel at the level of the constriction ring; and (8) avoidance, when possible, of exteriorization procedures.

It is our firm belief that although all the answers are not yet available, adherence to sound principles based upon an intelligent appreciation of what is known of the morbid physiology in strangulation obstruction, and the resultant improvement in surgical results, indicate that good management can further lower existing mortality rates.

Dr. Harold Laufman:—I should like to thank Dr. Wangensteen for his significant remarks. We are not interested in advancing the enzyme factor as an important one in the toxicity of strangulation obstruction; we are interested in investigating it. We are fully aware of all the associated factors involved in a toxicity of any type.

The use of antibiotics, although very important, has been shown to have certain limitations.

I want to quote one experiment which showed the limitations of antibiotics in strangulation obstruction. We produced a standard strangulating lesion of the intestine in a group of dogs. The strangulation was allowed to remain until the limits of viability were reached. We then released the strangulation and gave massive doses of penicillin. Every one of the animals so treated

developed some abdominal or intestinal complication, indicating that the greater the degree of destruction of tissue, the longer is the pathway to recovery. Thus, even though bowel may recover, it may be crippled. Therefore, loops of questionable viability had better be resected.

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DIFFERENTIAL DIAGNOSIS OF JAUNDICE BY LABORATORY TESTS*†

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Chicago, Ill.

A large number of individual laboratory tests have been devised to assist in the differential diagnosis of jaundice. New single tests are reported frequently but their description or evaluation do not appear to be the most urgent problem today. The greater challenge is the organization of the available tests into a system which permits analysis of the individual patient, correlating the abnormal physiology with the clinical manifestations. In recent years several such systems have been described, and the term "liver profile" has been coined by Watson and his co-workers[1]. I would like at this time to discuss the system which has been found useful in our institution and to analyze the basis of some of the tests for which, in the past few years, new information has become available. In this analysis it may be of value first to discuss a somewhat simplified classification which Dr. Schaffner and I have been applying (Table I).

Jaundice without impairment of bile flow may be due either to overproduction of bile pigment, as in a hemolytic syndrome, or due to a retention of bile pigment (faulty excretion of serum bilirubin by the liver), as in familial jaundice in young persons. Neither of these conditions offers much differential diagnostic difficulty and is usually recognized by clinical and laboratory examination. Impairment of bile flow may be mechanical, due to obstruction, or functional. The obstructive type is commonly caused by an extrahepatic process, but it has been repeatedly maintained that even the smallest bile ducts within the liver may occasionally become mechanically obstructed. Functional impairment of the bile flow, in most instances due to an altered function of the epithelial liver cells, is usually associated with alteration of the Kupffer cells. However, evidence tends to support the theory recently presented by Watson and Hoffbauer[4] that functional impairment of the smallest bile ducts (cholangioles) may result in a backflow of bile from the biliary system into the blood, even if no anatomical changes are visible. This questionable mechanical obstruction at the level of the cholangioles or their functional impairment has been termed "cholangiolitis". In extrahepatic obstruction as well as in "cholangiolitis", the problem is that of regurgitation of bile from the biliary tract into the blood stream. In the hepatocellular lesion with associated Kupffer cell involvement, parenchymal dysfunction is the basic problem. Laboratory tests are available to recognize both the phenomenon of regurgitation and parenchymal involvement. However, this information does not give the desired differentiation between surgical jaundice, due to tumors, stones and strictures, and medical jaundice, due to primary hepatitis and cirrho-

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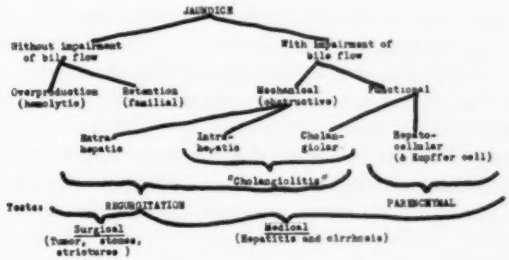
sis, since "cholangiolitis" as an intrahepatic process also belongs to the medical group and thus represents the source of much confusion.

Many tests have been used in the differential diagnosis of jaundice. It may be appropriate to discuss now the basis of a few which are at present most widely used and for which new information has recently become available. This is especially true of the flocculation tests which test the stability of serum proteins in different solutions. Tendency toward flocculation, precipitation or turbidity is, in general, increased with (a) decrease in or alteration of serum albumin and/or alpha globulin, both presumably formed by the liver cells; (b) increase of the serum gamma globulins which are formed by the Kupffer cells and other reticuloendothelial cells, and (c) increase in serum lipids. Tendency toward flocculation is depressed if there is present in the serum a factor which seems to leak back into the blood in regurgitation jaundice; this factor has tentatively been identified as lecithin[5]. In damage of the parenchymal liver cells, serum albumin and/or alpha globulin are reduced. This is supported by the observation that in such

TABLE I

CLASSIFICATION OF JAUNDICE



conditions the cytoplasm of the liver cells fails to show the characteristic basophilia, which is due to the presence of pentose nucleic acid and has been considered an indication of the site of protein formation. In parenchymal damage the serum gamma globulins are usually increased as a result of proliferation of the Kupffer cells, the cytoplasm of which is now strongly basophilic. However, gamma globulin increase occurs in most chronic infections and is not specific for liver disease. In contrast to this, the gamma globulin fails to rise significantly in biliary regurgitation because the Kupffer cells are loaded with bile pigment and the depressing regurgitation factor is increased.

Utilization of these phenomena permits the use of a flocculation profile which in our institution is based on the use of four tests: (a) cephalin cholesterol flocculation of Hanger[6] which depends mainly upon reduction of serum albumin and/or alpha globulin and less so upon increase of gamma globulin; the flocculation is somewhat depressed by the regurgitation factor. It is abnormal in parenchymal cell damage and normal in noninfected biliary regurgitation,

even in the presence of liver cell damage, but rises in biliary infection due to formation of gamma globulins outside the Kupffer cells. (b) Thymol turbidity of Maclaglan[7] which, in principle, depends upon the same factors except that an elevation of serum lipids and lipo-proteins is also important. The test, in general, is abnormal under similar circumstances as the cephalin flocculation. (c) Zinc sulfate turbidity of Kunkel[8] which depends mainly upon elevation of gamma globulin but is depressed by the regurgitation factor. It is elevated in liver cell damage, especially cirrhosis, but also in other chronic inflammations and the elevation is, therefore, not specific for liver disease. However, zinc sulfate turbidity is normal and sometimes even below normal in most instances of biliary regurgitation, even if liver cell damage and some biliary infection are present. In our hands low or reduced zinc sulfate turbidity has been one of the most significant laboratory findings in jaundice. (d) Gamma globulin turbidity (ammonium sulfate turbidity of Huerga and Popper[9], which depends solely upon gamma globulin elevation, is elevated in liver cell damage, especially in cirrhosis and other chronic infections. This finding is, therefore, not characterstic, but an elevation may be helpful in the recognition of the transition of hepatitis into cirrhosis when the results of other flocculation tests may return to normal.

In recent years serum alkaline phosphatase has been the subject of much argument[3], although its diagnostic significance is beyond any doubt. The enzyme is found in many body cells. It is released to the blood from the osteoblasts (and is, therefore, increased in bone diseases and in childhood) as well as from the intestine. Its activity rises slightly in every type of liver cell damage, probably due to an associated regurgitation of slight degree. A marked rise, however, is characteristic for biliary regurgitation and, according to some, is due to piling up in the blood of phosphatase which is formed outside the liver and is normally excreted in the bile, while others assume an excessive formation by the liver as the cause of the elevation (possibly cholangiolar cells under the stimulation of regurgitation). It should be noted that serum alkaline phophatase is elevated in carcinoma of the liver and in some cirrhoses, probably due to excess formation.

Serum cholesterol is formed by the liver cells and some is excreted in the bile. Therefore, the total serum cholesterol is reduced in very severe liver damage and is increased in regurgitation, partly due to piling up but more so due to excess formation under the stimulation of regurgitation. In some instances of regurgitation a very marked elevation may occur which may even be associated with xanthoma formation. About two-thirds of the total serum cholesterol (more than 60 per cent) is esterified by the liver or by the gut under the influence of the liver. Therefore, the cholesterol ester/total cholesterol ratio is reduced in liver cell damage. When the total cholesterol is normal, only severe liver cell damage reduces the ratio, whereas with elevated total cholesterol as in regurgitation (e.g., in surgical jaundice), slight liver cell damage reduces the ratio. This makes the determination particularly useful in the recognition of liver cell damage in surgical conditions.

Urinary urobilinogen is formed by intestinal bacteria acting on bilirubin. It is partly reabsorbed from the intestine and partly excreted in the stool. The absorbed urobilinogen is re-excreted into the bile (enterohepatic circulation) and only small amounts appear in the urine. In the presence of hemolysis, more bilirubin spills into the intestine and more urobilinogen is found in urine and stool. In the presence of liver cell damage, the enterohepatic circulation is interrupted because the liver is unable to excrete urobilinogen and its urinary excretion increases. In regurgitation two possibilities exist: (a) with complete obstruction, e.g., in the presence of tumors, no bilirubin enters the intestine and no urobilinogen is found in stool and feces; (b) without complete obstruction, increased or spiking urinary urobilinogen levels may be found due to intermittent obstruction as it is produced by ball-valve action of stones.

Utilizing the points which have just been discussed, the following laboratory findings are indicative of parenchymal liver damage: abnormal cephalin flocculation, increased thymol turbidity, increased zinc sulfate turbidity and gamma globulin turbidity (not specific), albumin reduction, reduced cholesterol ester/total cholesterol ratio (especially if associated with regurgitation), increased urinary urobilinogen, reduced hippuric acid synthesis, low serum (choline) esterase, reduced galactose tolerance or galactose removal constant, bromsulfalein retention (indicative also of disturbed hepatic circulation, of little value in jaundice), poor response of prothrombin time to Vitamin K. Because of the possibility of biologically false positive tests (an almost 10 per cent probability), two different tests should yield abnormal results before assuming that parenchymal involvement is present. Liver biopsy is also a good procedure for the recognition of liver damage, if the condition is diffuse.

The following laboratory findings indicate the presence of regurgitation jaundice (cholangiolar or hepatocanalicular involvement): elevated total serum cholesterol, marked elevation of serum alkaline phosphatase, depressed zinc sulfate turbidity and, depending upon the degree of associated biliary obstruction, reduced or absent urinary urobilinogen and reduced or absent fecal urobilinogen.

How can extrahepatic biliary obstruction due to surgical jaundice be differentiated from "cholangiolitic" cirrhosis or hepatitis (medical jaundice)? Biochemical laboratory tests are of almost no value here. Liver biopsy, especially in protracted cases, may be helpful. It is only in extrahepatic obstruction that bile plugs in bile extravasates (bile lakes) around interlobular bile ducts are found in the portal triads, since in "cholangiolitis" the process occurs proximal to the interlobular bile ducts. These processes, however, require some time for development and may not occur uniformly. Thus, only their presence in the liver biopsy specimen is diagnostic. Occasionally the history helps in the differentiation. For instance, exposure to arsenicals has a tendency to cause "cholangiolitis". The best differentiation, however, is possible at laparotomy when a narrow common and hepatic duct in a patient with regurgitation jaundice suggests

intrahepatic involvement due to "cholangiolitis". The main exception to this is carcinoma at the bifurcation of the hepatic duct at the hepatic hilus, a condition for which surgical intervention is practically impossible. In "cholangiolitis" additional surgery, such as drainage of the gallbladder or common duct, should be avoided.

If we now try to apply the presented facts to the differential diagnosis between surgical and medical (nonhemolytic) jaundice, we arrive at thought processes which can be presented in the following schema:

A. If parenchymal damage is present (more than two laboratory tests having yielded abnormal results) and regurgitation is absent, the case is considered medical with the following exceptions:
   1. Incomplete obstruction due to a stone which is recognized by spiking urinary urobilinogen excretion in follow-up studies.
   2. False positive tests as may be found in a patient in whom an abdominal mass or a history of colic are the only clues to the diagnosis.

B. If evidence of parenchymal damage is absent and if regurgitation is present, the case is considered surgical, the exception being "cholangiolitis" which is recognized possibly by liver biopsy and definitely by laparotomy.

C. If evidence of both parenchymal damage and regurgitation is present, one should follow the results of the flocculation tests. If the results of these tests disagree, the most significance should be given to a negative zinc sulfate turbidity, and then to a positive cephalin flocculation and thymol turbidity. Therefore:
   1. If cephalin flocculation or thymol turbidity in this group is positive, the case is medical with the following exceptions:
      a. Secondary bacterial infection of an extrahepatic biliary obstruction in which excessive gamma globulin production takes place outside the Kupffer cells. The condition is recognized as surgical jaundice by the clinical evidence of septicemia, such as chills, fever and leucocytosis.
      b. False positive tests. Here an abdominal mass or a history of colicky attacks may lead to the correct diagnosis.
   2. When the zinc sulfate turbidity is negative, the case is considered surgical with liver cell damage produced by prolonged biliary obstruction. The exceptions are the rare cases of toxic and chemical hepatitis in which Kupffer cell proliferation and gamma globulin elevation are absent and which can usually be suspected from the history.

What help do the laboratory tests give in the differential diagnosis between acute hepatitis and cirrhosis? As a rule, Kupffer cell mobilization and other signs of mesenchymal reaction are far more marked in cirrhosis than in hepatitis.

Therefore, the elevation of the zinc sulfate turbidity is out of proportion to the abnormality of the cephalin flocculation and especially thymol turbidity. Consequently a high zinc sulfate turbidity/thymol turbidity ratio speaks for cirrhosis. However, liver biopsy is probably the best procedure for this differentiation, since only rarely is a cirrhotic area missed in the small core of the biopsy needle.

What help do the laboratory tests give in the differential diagnosis between benign biliary obstruction, due to stones and strictures, and malignant biliary obstruction? Permanent absence of urobilinogen from the urine is more common in malignancy in which obstruction is progressive. A rare exception is a temporary relief of the obstruction at the papilla of Vater by sloughing off of necrotic cancerous tissue. Spiking urinary urobilinogen levels speak for stones (ball-valve effect) or strictures (intermittent obstruction). As a rule, parenchymal damage is more marked in malignancy (the cholesterol ester ratio is especially low) but this may be obscured by a purulent infection in a benign lesion. In general, the laboratory tests are of little help. It should be stressed that blood in the stool may be found also in jaundice caused by benign biliary obstruction.

What are the laboratory indications of severe hepatic failure? Marked prolongation of prothombin time, marked drop of cholesterol ester/total cholesterol ratio, low total serum cholesterol, drop of previously elevated alkaline phosphatase, rapid rise of serum bilirubin, marked drop of serum esterase, elevation of serum nonprotein nitrogen, positive Millon reaction for tyrosin in urine, and drop of previously elevated thymol turbidity.

The presented systematic applications of the laboratory tests in the differential diagnosis of jaundice are surely not fool-proof but they should offer a system of assistance if used in conjunction with the clinical findings and the history of the jaundiced patient.

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EDITORIALS

Jaundice

Careful clinical evaluation of jaundiced patients is of great importance, since blind acceptance of results of liver function tests may be misleading. The alkaline phosphatase and flocculation tests are helpful in deciding whether jaundice is hepatocellular in origin or caused by extrahepatic bile duct obstruction. Phosphatase activity of 30 or more King-Armstrong units strongly suggest obstructive jaundice. Conversely, positive results of flocculation tests indicate intrinsic hepatic disease. Use of this combination provided correct diagnosis in 72 per cent of 54 jaundiced patients at Guy's Hospital, London. In 3 cases, the results were misleading and in 12, the two tests were valueless. Alkaline phosphatase is apt to exceed 30 King-Armstrong units with malignant biliary obstruction.

Samuel Weiss

Baker, G. P., Guy's Hospital Reports, **100**:342, 1951.

Pancreas

In the diagnosis of cancer of the pancreas, the roentgenologic evidence is distinctly less valuable than is inspection of the stools for bulkiness and free fat, microscopic examination for muscle fibres, chemical analysis after a test diet, the secretin test and demonstration of abnormal amounts of pancreatic enzymes in the blood.

When pancreatic insufficiency results from carcinoma in the head of the pancreas or ampulla of Vater, the feces are extremely bulky, clay colored and pultaceous, a condition easily recognized by comparing the twenty-four hour collections with normal stools.

Discrete fatty lumps resembling butter or cream in the stools occur only with pancreatic insufficiency. Such a finding excludes other causes of pale bulky stools, confirms the diagnosis and is conveniently demonstrated by having the patient eat extra butter or olive oil, also the microscopic findings of many indigested muscle fibres in the stool, with ends which are sharp or square, and the transverse striations well preserved are significant.

Occult blood in the feces does not distinguish pancreatic carcinoma from other gastrointestinal disease. A 3 day test diet, however, with known amounts

of protein, carbohydrate and fat is marked with carmine or charcoal and the nitrogen and fat content of the dried stools determined, will aid in the detection of pancreatic involvement.

Fever and leucocytosis are frequent with advanced carcinoma of the pancreas. Serum diastase and lipase values are often normal with cancer of the pancreas but elevation indicates pancreatic disease, hence the test should be employed when possible.

Carcinoma of the body or tail of the pancreas seldom produces pancreatic insufficiency and pain and weight loss may be the only symptom. Persistent pain is typical and may be in the back, chest or abdomen.

SAMUEL WEISS

Brown, Randolph, K., Mosely, Vince, Pratt, T. D., and Pratt, Joseph H.: The early diagnosis of cancer of the pancreas and on the clinical and pathological study of one hundred autopsied cases. Am. J. M. Sci., **223**:349, 1952.

ABSTRACTS

ESOPHAGUS

CARDIOPLASTY IN THE SURGICAL TREATMENT OF ACHALASIA OF THE ESOPHAGUS: Arne Malm, Scandinav. J. Clin. & Lab. Invest. 3:89.

Eighteen patients with achalasia of the esophagus were subjected to transpleural cardioplasty and followed up for 6½ years to 8 months. The method gave relief from the characteristic symptoms of achalasia and provided a good passage between the esophagus and the stomach. However, some time after the operation (2-4 months or more) other symptoms, which seemed to be referrable to the operation, occurred. These symptoms were dyspepsia and anemia. Dyspepsia might feasibly be explained by the surgical intervention rendering the closure mechanism of the cardia incompetent and thereby permitting the acid gastric juice to regurgitate up into the esophagus. It was, however, difficult to find an explanation for the anemia, which was of hypochromic type and reacted promptly to iron therapy. The earlier follow-up examinations gave no clue but certain observations – formation of peptic esophagitis and granulation tissue in the suture line in the cardiac region as well as periodically positive reactions to the Weber test and the benzidrine test – suggested hemorrhagic anemia as the most possible explanation. In an endeavor to elucidate the problem, a more thorough clinical follow-up and experimentall studies were performed.

The experiments on dogs showed that if the closure mechanism of the cardia in intact dogs is operatively rendered incompetent or bypassed, peptic digestion of the esophageal mucosa with resultant esophagitis and esophageal peptic ulcer will occur within about three months. These changes were found to be capable of producing chronic hemorrhage capable of causing marked anemia. The experiments seem to support the assumption that the granulation tissue sometimes seen developing in the cardiac region after cardioplasty is due to poor healing in this region. The friction of trauma from the passage of food and the peptic factor may prevent also secondary healing. In this manner also a formation of chronic granulation tissue might provide a source of bleeding.

FRANZ J. LUST

STOMACH

LATE RESULTS AFTER TOTAL GASTRECTOMY: ReMine and Priestley. Surg. Gynec. & Obst. 94:519 (May), 1952.

One hundred and eighty-five cases in which total gastrectomy was performed have been reviewed. A malignant lesion was present in a hundred and seventy cases and in the remaining fifteen cases the lesion was benign. Technical considerations such as the type of anastomosis, the establishment of jejunojejunostomy, and the postoperative use of an indwelling nasal catheter had little effect on the surgical risk so long as a well-chosen and carefully executed operative procedure was performed.

Six patients, each of whom was subjected to total gastrectomy for a benign lesion, were followed five years after operation; four of these were alive. Fifty patients who had total gastrectomy performed for a malignant lesion of the stomach were followed for five years. Nine (eighteen per cent) of these were alive. Half of the patients who survived total gastrectomy for five years were able to perform their usual work. Half of the remaining patients were able to work part-time. All required treatments for anemia. Approximately two-thirds of the patients who survived five years regained their preoperative weight.

J. R. VAN DYNE

ON THE TREATMENT OF ULCUS VENTRICULI AND DUODENI: BY "CYREN" — A IMPLANTATION: W. Sandrowski. Med. Welt. No. 16, page 529.

Since August 1947 the author has carried out "Cyren" – A implantations in more than 200 patients for the treatment of ulcus ventriculi et duodeni and other gastric diseases (gastritis, gastroduodenitis, ptosis, cicatrized alterations of the duodenal bulb often accompanied by stenosis and difficulties in evacuation, as well as ectasia and atony) with considerable success. The treated persons comprised men of all age-

groups and in single cases women beyond the menopause – young women were given intragluteal injections of "Cyren" – B crystalline suspensions (5 mg.). Favorable clinical results have been achieved with 1 or more "Cyren" – A implantations in 84 per cent of out-patients and those treated in the clinics.

Special advantages of "Cyren" – A implantations-therapy are abolition of lingering series of injections, of the more or less strict diet, and of confinement to bed, so that the patients can pursue their daily duties.

Clinical cure occurred in most cases after one "Cyren" implantation (10 mg.). Occasional complaints which mostly set in 3 - 5 months after the effect of the implantation had faded away, could promptly be removed by a second implantation. Hitherto more than 2 - 3 implantations have scarcely been necessary.

A special inclination to relapses and remarkable resistance to therapy due to irregular and insufficient nutrition has been observed in motorists, or in patients who were vegetatively stigmatized.

Pains due to swelling of the breasts discontinued within 2 - 5 days. Besides swelling of the nipples side-effects (atrophy of the testicles, diminution of potency and libido) were not to be observed.

FRANZ J. LUST

GASTRIC ANTACID AND ANTISECRETORY DRUGS: A Survey Based Primarily on their Effect Upon Gastric Secretion in Man: J. B. Kirsner, Walter L. Palmer, E. Levin, and A. P. Klotz. Ann. Int. Med. 35:785-811 (Oct.), 1951.

The present survey indicates that calcium carbonate appears to be the most effective of the many antacids in current use. It does not cause alkalosis, and its constipating effect can be neutralized with laxative addition. However, control is maintained during administration only, and with its use nocturnal gastric secretion is still a problem. The results with atropine are variable and its effect may be due to prolonged gastric emptying. Synthetic atropine-like compounds offer no particular advantage. In contrast the results with the other cholinergic blocking agents are promising. Hexamethonium compounds have yielded promising preliminary results. Banthine has yielded encouraging results although recurrent ulcers have been noted on banthine therapy. There is no evidence to indicate that these agents produce the physiologic effect to be expected from complete vagotomy.

J. R. VAN DYNE

ROENTGENOLOGICAL DIAGNOSIS OF THE DUODENUM INVERSUM: W. Hirsch, and O. Muench. Fortschr. Geb. Roentgenstrahlen 75:445 (Oct.), 1951.

After a genetic definition of the conception "duodenum inversum" a review of the literature and a series of their own cases are presented. It is stated that from a genetic point of view these cases cannot be called as real duodenum inversum. They are generally anomalies conditioned by incomplete rotation of the duodenum or by changes of the position of the organs following gastroptosis or kyphoscoliosis in a mobile duodenum. To this collection of cases is added one case, in which the diagnosis of partial inversion of the duodenum is genetically and roentgenologically justified, as it meets the criteria which must be present in a critical study of a duodenal inversion.

FRANZ J. LUST

A CONSIDERATION OF THE PRESENT STATUS OF SIMPLE SUTURE IN THE TREATMENT OF ACUTE PERFORATED GASTRODUODENAL ULCERATION: Mage & Payson. Surg. Gynec. & Obst. 94:581 (May), 1952.

It is concluded, following the authors' study, that surgical exploration is favored as well as the use of simple suture in all early acute perforations, whether the diagnosis is suspected or definitely proved, unless the condition of the patient contraindicates a laparotomy or the use of an anesthetic. Likewise, if a case is seen after a lapse of twelve to twenty-four hours without convincing clinical signs of localization, this approach is still preferred providing no operative contraindication exists. If the clinical evidence in such delayed cases indicates a definite spontaneous containment of the effects of perforation, the authors are prepared to entertain the use of the non-

operative method. Their decision to a large degree would be determined by the condition of the patient. Finally they are prepared to modify their preference for the use of simple suture in acute perforations which occur within or adjacent to chronic callous penetrating ulcer, particularly at the site of the re-entrance angle of the stomach. In such cases, in which closure may prove difficult or uncertain, a partial gastrectomy may be justifiable providing the condition of the patient is favorable and the experience of the surgeon is adequate.

J. R. VAN DYNE

GASTROINTESTINAL TRACT

EARLY ROENTGEN DIAGNOSIS IN ACUTE BLEEDING FROM THE UPPER GASTROINTESTINAL TRACT: Max Ritvo, Thomas P. Cotter, and Norman Zamcheck. Am. J. Roentgenol. 66:728 (Nov.), 1951.

The authors studied 52 patients. Emergency roentgen examination of the esophagus, stomach and duodenum was carried out as early as possible. Roentgen studies were performed in 42 per cent of the patients within 24 hours; in 63.5 per cent within 48 hours; and in 83 per cent in less than 72 hours after admission to the hospital.

The roentgen studies were not performed in routine fashion but were individualized according to the condition of the patient. It was the authors' practice to make the examination as complete and detailed as possible. The patients were divided into three categories: those too ill to stand (3 patients); those able to stand but whose condition precluded the use of mechanical pressure (44 patients); and those in whom complete roentgen study including palpation and mechanical pressure was possible (5 patients).

Small amounts of opaque meal proved more satisfactory for the demonstration of most lesions. The roentgen technics are discussed. Only four patients of the entire group showed evidence of continued or recurrent bleeding after examination. In no instance were there any serious complications or sequelae attributable to the roentgen studies. The early examination is of great benefit to the patient.

FRANZ J. LUST

ASYMPTOMATIC GASTRIC MUCOSAL PROLAPSE: Emanuel J. Levin, and Benjamin Felson. Radiology. 57:514 (Oct.), 1951.

The authors performed roentgenological studies of the upper gastrointestinal tract in 100 patients who had no gastrointestinal symptoms.

Gastric mucosal prolapse was encountered in 18 cases. The prolapse was slight in ten, moderate in five, and marked in three patients. No significant increase in frequency of prolapsed mucosa was encountered in any particular systemic disease.

Because of the high incidence of this finding in patients without symptoms, Levin and Felsen concluded that the clinical significance of gastric prolapse has been overemphasized, and that it is seldom the cause of symptoms.

FRANZ J. LUST

PLASMA CALCIUM AND INFLUENCING FACTORS IN SEVERE INFANTILE GASTROENTERITIS: Niilo Hallman, Hilkka Taehkae, and E. K. Ahvanainen. Ann. med. int. Fenniae 40:1, 1951.

The authors reported studies on plasma calcium and symptoms suggesting tetany in 55 patients with severe infantile gastroenteritis. Twenty were treated without potassium and showed a mortality rate of 34 per cent. Thirty-five were subjected to routine potassium treatment; mortality rate 17 per cent. A lowered calcium level in the plasma as well as tetanic manifestations occurred with about equal frequency in both these groups. Among the fatal cases the calcium was lowered (under 9 mg. per cent) after the first days of treatment in 10 of 13 cases, and among the recoveries in 24 cases out of 42. The fall in the calcium often occurred simultaneously with the increase in the alkali reserve, and especially if it rose above the normal levels. The bicarbonate therapy (10-25 ml 1.3 per cent solution/kg.) referred to, probably had its share in the elevation of the alkali reserve above the normal, although it can occur

even without bicarbonate therapy. If plasma proteins are low, the calcium is lowered more often than if they are high or normal. Tetanic manifestations occurred in 36 patients and in 26 of them the plasma calcium was lowered. This was found in all those who died.

The cause of tetanic manifestations can be the ionization of calcium which may have undergone changes for some reason. On the other hand, consideration must also be given to disorders of the central nervous system resulting from different causes. A case is described which recovered from severe gastroenteritis, was later affected with convulsions and died of pneumonia. The brain revealed marked atrophy, slight degenerative changes and small calcifications.

The rise in nonprotein nitrogen in the initial stage of the disease does not have any pronounced effect on the subsequent lowering of calcium. Renal changes bearing a close resemblance to lower nephron nephrosis do not explain the fall in calcium.

FRANZ J. LUST

INTESTINES

MULTIPLE LOCALIZATIONS OF LYMPHOSARCOMATOSIS (KUNDRAT'S DISEASE) IN THE DIGESTIVE TRACT: R. Cattan, R. Carasso, P. Frumussan, H. Hoppeler, P. Pariente and Ch. Zerah. Arch. des Mal. de l'Appar. Digest. 12:1289, 1951.

In this well-illustrated article, the authors describe almost identical observations carried out with three patients suffering from Kundrat's disease. In all three cases, the apparent onset was by way of the pharynx and the ganglions of the neck. A biopsy revealed on each occasion that it was a question of lymphocysto-lymphoblastoma.

In the first case, the radiological examinations of the stomach showed extremely curious images of hypertrophic gastritis which diminished, without disappearing entirely, under the effect of radiotherapy. On rectal examination, a localization in the anorectal region, which is clinically silent, was discovered. The autopsy later revealed that the gastric submucosa was infiltrated throughout by the malignant process, whilst the mucous membrane was, in places the seat of a malphigian metaplasia. Furthermore, the spleen and kidneys were the seat of multiple metastases.

In the case of the second patient, after a spectacular improvement of the condition of the pharynx due to radiotherapy, gastric pains and a palpable tumor of the umbilical region appeared. Radiographies showed a magnificent tumoral image of the second portion of the duodenum. There again radiotherapy proved effective. Later some slight symptoms drew attention to the anorectal region. Rectal examination and rectoscopy revealed a relatively soft granulating mass a few centimeters away from the anus. Radiotherapy by way of the sacral tract caused a rapid disappearance of the tumor which left no trace at the autopsy. Death occurred due to hemorrhage following incision of a superficial abscess.

With the third patient, the localization in the stomach after a complete abatement of the pharyngeal symptoms resembled an ordinary cancer of the lesser curvature. There again radiotherapy was momentarily amazingly effective. Furthermore, 13 cm. away from the anus, there was a rectal localization which was responsible for disorders which had long been wrongly attributed to chronic amebiasis.

The authors insist on the frequency of multiple metastases of the digestive tract and notably on the necessity of a systematic proctological examination in the case of Kundrat's disease.

MALIGNANT POLYPS OF THE RECTUM AND SIGMOID: Fisher and Turnbull. Surg. Gynec. & Obst. 94:619 (May), 1952.

A descriptive classification of carcinoma arising in a polyp is presented. Malignant change, limited to the glandular structures of the polyps without evidence of invasion of the lamina propria, is considered as carcinoma *in situ*. A lesion demonstrating invasion of the lamina propria of the polyp but without invasion of the muscularis mucosa or lymphatic and vascular channels is termed superficial carcinoma. The presence of invasion of muscularis mucosa and/or lymphatic and vascular phases is characteristic of invasive carcinoma. The occurrence of a desmoplastic tumor stroma in invasive carcinomas has been a valuable histologic aid in establishing this degree of malig-

nancy. Carcinoma *in situ* and superficial carcinoma arising in a polyp in the rectum and lower sigmoidcolon are treated locally. Fourteen patients in this series with such a lesion have been followed from two to ten years without recurrence of their disease.

Invasive carcinomas arising in polyps are treated by abdominoperineal resection except in the aged or debilitated, or in the patient who is a poor surgical risk.

J. R. VAN DYNE

THE ROENTGEN APPEARANCE OF INTESTINAL POUCHES FOLLOWING LATERAL ANASTOMOSIS: Hyman R. Senturia and Carl J. Heifetz. Am. J. Roentgenol. 67:227 (Feb.), 1952

Attention is directed to the roentgenologic appearance of blind pouches following lateral intestinal anastomoses. Six cases in which blind pouches were demonstrated roentgenologically are recorded. Five of these occurred in the small intestine and one in the large intestine. Three of the patients had symptoms directly attributable to the presence of the pouch. Obscure gastrointestinal symptoms such as colicky abdominal pain, distention, nausea, and vomiting may be explained by the roentgen demonstration of a blind intestinal pouch. Macrocytic anemia may also be caused by this abnormality. Attention may be directed to the pouches by barium retained within them after evacuation of a barium enema or during barium studies on the small intestine. Unwarranted surgery can be avoided or curative surgery can be performed if the correct interpretation of the roentgen findings is made.

FRANZ J. LUST

RADICAL ABDOMINAL PROCTOSIGMOIDECTOMY WITH PRESERVATION OF THE ANAL SPHINCTER: Rheinlander and S. Welch. Surg. Gynec. & Obst. 94:550 (May), 1952.

A technic for resection of cancer of the rectosigmoid with preservation of the anal sphincter was described. Special features of the procedure include a radical superior dissection and excision of the site of lymphatic metastases and a low rectal amputation with anastomosis. A serious complication of operative procedure was rectal stricture. Stricture, however, is a recognized complication of low rectal anastomosis anyhow. Swenson has reported one stricture in thirty-one patients with this type of primary resection performed for Hirschsprung's disease. The fact that the anal sphincter is not cut and that the rectum is intact to the level of the levator ani is responsible for the good functional results achieved.

J. R. VAN DYNE

ARGENTAFFIN TUMOR OF THE ILEUM WITH PERFORATION: Ian S. Stewart, and G. Russel Thomson, Brit. M. J. page 1316 (Dec.), 1951.

A case of perforation of the small intestine resulting from one of three argentaffin tumors of the ileum is described. Treatment was by excision of all three, restoration of the continuity of the gut, and closure of the abdomen without drainage after liberal application of sulfanilamide powder to the operation sites.

The patient recovered uneventfully. No roentgenologic studies are reported. No mass could be palpated on abdominal examination, but during vaginal examination, a hard tender mass was felt above the right fornix.

FRANZ J. LUST

ADENOCARCINOMA OF THE LARGE INTESTINE ASSOCIATED WITH ULCERATIVE COLITIS, CLINICAL STUDY OF 73 CASES: W. B. Shands, M. B. Dockerty, and J. A. Bargen. Surg. Gynec. & Obst. 94:302-310 (March), 1952.

The risk of development of a secondary adenocarcinoma of the large bowel in cases of ulcerative colitis increases with the duration of the disease. In the series of 73 cases, only 8, or 11 per cent had ulcerative colitis for less than 5 years before the secondary adenocarcinoma was discovered. The carcinomas which develop are often high grade (39 graded 3 or 4 Broders' method). The prognosis is grave: there were only 2 five year survivors in the series and one subsequently died from the effects of the carci-

noma. Multicentricity of the adenoma was striking (in 21 of the 40 resected specimens) and there was a high incidence of pseudopolyposis (76 per cent) in these cases; and a low incidence in cases which were not multicentric. It is concluded that chronic ulcerative colitis which has been quiescent for 10 years or more gives no assurance against the development of a secondary carcinoma.

J. R. VAN DYNE

NEURINOMA OF THE RECTUM: Edison De Olivera, Pedro De Souza Campos Filho. Rev. Brasil. Gastroenter. 3:275 (May), 1951.

A review of all neurinoma cases of the literature is presented. Only one case of rectal neuroma, two of rectal neurofibroma, one of sigmoidal neurofibroma, one case of a neurofibroma of the presacral space and one Schwannoma of the rectovaginal septum were found. Two different ways of clearing these tumors are found, one as raised from the Schwann cells and the other, as originating from the mesoderma, formed by connective tissue cells. A definition of each type of these tumors is presented. The aspect of malignant potentiality of the neurinomas is discussed. The authors believe that they become malignant.

One successfully operated case is reported, as well as its roentgenological appearance and anatomopathological illustrations are given.

FRANZ J. LUST

PSYCHOSOMATIC STUDY OF ULCERATIVE COLITIS: Walter I. Tucker. Lahey Clin. Bull. 7:78-82 (Jan.), 1951.

Emphasis is made on the advisability of avoiding extensive probing in regard to emotional factors during the acute stages of the disease. The patient needs encouragement and support and someone on whom he can depend. There is no characteristic personality, but traits of excessive sensitiveness, conscientiousness, scrupulousness, inferiority feelings and ambitiousness are prominent. It is not contended that emotional abnormalities constitute the cause of ulcerative colitis; such abnormalities occur without the development of ulcerative colitis and ulcerative colitis occurs in patients without such abnormalities. It is pointed out that other factors such as constitutional predisposition, infections, and diet have an obvious bearing and that all factors must be considered in this disorder.

J. R. VAN DYNE

ROENTGEN FINDINGS IN ILEOJEJUNITIS: Richard H. Marshak, A. I. Friedman, B. Wolf, and B. B. Crohn. Gastroenterology 19:383 (Nov.), 1951.

The authors report 49 cases. The roentgen features closely follow the pathologic changes, and have been divided for the purpose of classification into nonstenotic and stenotic forms. 38 cases were listed as nonstenotic and 11 as stenotic. The roentgen features of the nonstenotic type of ileojejunitis in this series are blunting and thickening of the mucosal folds, and as the process proceeds by the presence of one of several types of abnormal pattern. These are designated for convenience as cobblestoning, reticulation, and cast form. These mucosal changes are associated with local diminished mobility, straightening of the loops of bowel and later rigidity of the involved segments of small intestine, wide spacing between the loops and finally, narrowing of the lumen. On occasion, the appearance of pseudodiverticula is noted and rarely, large fingerprint-like defects simulating intramural tumors.

The findings most frequently seen in the stenotic type of lesion are large areas of stenosis resembling rigid pipe stems with proximal dilatation. Disease may or may not be present in the dilated segments of bowel. The loops are widely separated and maintain a fairly constant relationship to one another. The mucosal pattern is usually reticulated or cast-like and numerous small filling defects may be noted. Skip areas are easily identified, masses are more frequent and fistulae may be demonstrated.

Differential diagnosis usually presents no problem. On occasion the roentgen features may be confused with the changes observed in the small bowel in lymphosarcoma and tuberculosis.

FRANZ J. LUST

BOOK REVIEWS

HUMAN BIOCHEMISTRY: Israel S. Kleiner, Ph.D., Professor of Biochemistry and Director of the Department of Biochemistry, New York Medical College, Flower and Fifth Avenue Hospitals; Formerly Associate, the Rockefeller Institute for Medical Research, New York. 695 pages with 83 text illustrations and five color plates. Third edition. The C. V. Mosby Co., St. Louis, Mo., 1951. Price $7.00.

Dr. Kleiner's third edition of Human Biochemistry is a welcome volume for all medical students of the first and second year classes, as well as for biologically trained students in other branches of our science colleges, for teachers and for practitioners of medicine and for medical and surgical residents and fellows in research, physiologists and biochemists.

This new edition briefly and quite informatively, although at times somewhat limited in scope, adequately presents the more important problems in human biochemistry.

Instructively and informatively presented are the sections on blood (pages 158-197), enzymes and digestion (pages 198-234), chemical changes within the large intestine, vitamins and foods (pages 243-323), nitrogen and carbohydrate metabolism (pages 344-417), lipid metabolism (chapter 17), including changes occurring in the liver where fat is carried for temporary storage, fatty livers, ketogenesis and ketosis, metabolism of cholesterol and abnormalities of lipid metabolism, mineral metabolism and water balance, "Hormones" (chapter 23) are interestingly discussed. Excellent up-to-date references to the literature follows each section. A very practical and helpful appendix of twenty-six pages (pages 639-664) completes the work, followed by a complete subject index of 30 pages. All in all, this textbook can be enthusiastically recommended to all medical students and instructors of the subject.

ESSENTIALS OF HISTOLOGY: Margaret M. Hoskins, Ph.D. and Gerrit Bevelander, Ph.D., New York University. 240 pages with 135 text illustrations and 2 color plates. Second Edition. The C. V. Mosby Co., St. Louis, Mo., 1952. Price $4.00.

This book is so well arranged and the informative and instructive material so well coordinated and correlated as to morphological characteristics of tissues and organs, as to structure and function, that it is a valuable aid to all college students studying histology, in the medical and dental schools and in the biological science courses.

This new edition is recommended for daily use at the table in the laboratory by all students of the subject.

THE PHYSICIAN EXAMINES THE BIBLE: C. Rainer Smith, B.S., M.D., D.N.B., 394 pages. Philosophical Library, New York, N. Y., 1950. Price $4.25.

This is an interesting little book. Of interest to the student, physician, nurse, churchman, historian and scholar. While there are a number of larger books available on the subject, such as Preuss (1911) (Talmudic and Biblical Medicine), Brim (Medicine in the Bible) etc., Macht's recent little monograph, as well as the well known works of Moritz Steinschneider (1817-1907). One of the greatest medical archivists Pagel, Neuberger, Gordon, H. Friedenwald, and others have contributed information of allied interests over the years. As the author well shows, the bible contains many references of medical interest. These references should be of interest to the bible student, as well as to the medical student and cultured medical practitioner.

KLING UND THERAPIE DER MAGEN—DARMKRANKHEITEN: Von Dr. F. Depisch Privatdozent an der Universitat. 297 pages with 16 illustrations. Springer-Verlag, Wien, 1951. Price $4.00.

This small volume of 297 pages (including eight pages of index) (in German) covers the gastrointestinal tract very briefly, including thirteen pages on diseases of the mouth and esophagus. Brief discussions are included on the anatomy and physiology of the stomach, gastritis, ulcer and cancer, brief comments on vagotomy, vagus and sympathetic resection, diseases of the intestines, sprue, colitis, chronic enteritis, obstipation, peritonitis, intestinal worms and amebic dysentery.

This is not a book for popular medical consumption in America where the advances in the management and diagnosis of many gastrointestinal conditions have been and are being made.

MEDICAL TREATMENT—PRINCIPLES AND THEIR APPLICATION: Edited by Geoffrey Evans, M.D., F.R.C.P., Consulting Physician, St. Bartholomew's Hospital, London. 1398 pages and 66 pages of index (subject). Butterworth & Co. (Publishers), Ltd., London, England. The C. V. Mosby Co., St. Louis, Mo., 1951. Price $20.00.

This English textbook of medicine edited by Dr. Evans contains contributions by fifty-three authorities, who have written sections on the topics in which each is particularly qualified by study and experience. This rather all inclusive text can be added satisfactorily as a good companion volume to the books and new editions edited and recently published by Meakins, M. G. Wohl, Loeb and Cecil, F. W. Price and Beckman's "Treatment".

This new work gives a good general survey of English medicine in relation to treatment.

THE APPROACH TO CARDIOLOGY: J. Crighton Bramwell, M.A., M.D., F.R.C.P., Professor of Cardiology in the University of Manchester, Physician to the Manchester Royal Infirmary with a foreword by A. V. Hill, C.H., O.B.E., Sc.D., F.R.S., Foulerton Research Professor of the Royal Society. 122 pages. Oxford University Press, New York, N. Y., 1951. Price $3.75.

This is an excellent "introductory course" of lectures for medical students, internes and residents and general practitioners interested in cardiology.

This informative and easily read monograph gives the fundamental all important essential principles of cardiology.

The many illustrations and legends are very helpful to the student. There are about forty-five references to the literature which the reader may refer to for a study of some of the original papers or textbooks.

This little monograph is recommended as a primer for students, general practitioners and internes.

THE KIDNEY—MEDICAL AND SURGICAL DISEASES: Arthur C. Allen, M.D., Pathologist, The James Ewing Hospital, Assistant Attending Pathologist, Memorial Cancer Center, New York City, Attending Consultant in Pathology, Veterans Administration Hospital, Bronx, New York. 583 pages. 1115 illustrations. Grune & Stratton, New York, N. Y., 1951. Price $.

This beautifully illustrated book by an experienced pathologist assures the owners of this volume reliable information, given in a very understandable manner. This book is easy to read and the legends with the very instructive illustrations help to impart important information.

The interpretations are clear and concise, the descriptions of the various conditions are adequate and most satisfactory to physician, surgeon, urologist, student and the general practitioner in particular.

This work is enthusiastically recommended by this reviewer as one of the best on the subject now available.

LEITFADEN DER LAPAROSKOPIE UND GASTROSKOPIE: Von H. Kalk, Prof. Dr. Med., Leitender Arzt der Inneren Abteilung der Stadtkrankenhause Kassel und W. Bruhl, Dr. Med. Habil. Chefarzt der Inneren Abteilung des Paulinen Hospitals Arolsen, unter Mitwirkung von W. Burgmann, Dr. Med., Chefarzt des Sanatoriums "Dr. Schorlemmer" Bad Gadesberg. 158 pages, with 82 illustrations, some in color. Georg Thieme Verlag, Stuttgart, Germany. Grune & Stratton, Inc., (New York, N. Y.), 1951. Price: 27 German marks.

The publisher is to be congratulated on this little monograph – the fine illustrations and good quality paper.

The authors have given the surgeons, endoscopists and gastroenterologists, who can read German, a fine informative monograph on the subject of laparoscopy and gastroscopy. While the volume consists of only 158 pages, it contains much helpful information. It would be a real contribution if

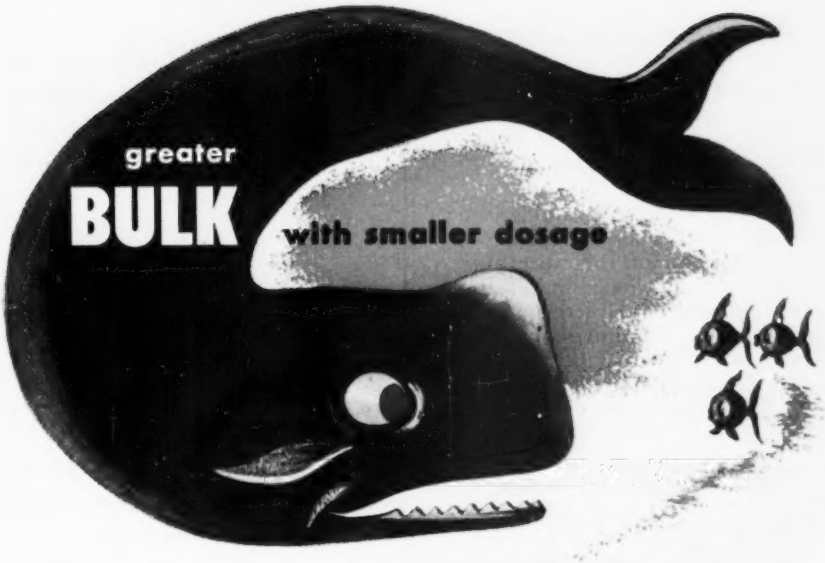
Grune and Stratton of New York could arrange for an English translation.

American and Canadian medical school libraries and all medical staff libraries should have this small monograph for the German reading students and staff members and teachers.

THE MICROKARYOCYTES, THE FOURTH CORPUSCLES AND THEIR FUNCTIONS: K. G. Khorozian, A.B., M.S., M.D. 969 pages, illustrated with reference and cross index. Meador Publishing Co., Boston, Mass., 1951. Price $12.00.

The book is divided into seven sections, each section is again divided into chapters and illustrated with microphotographs. It is a highly specialized subject that the author deals with and no doubt will be interesting to the research worker. However, the reviewer came across an item on page 379 which rather interested him. It deals with duodenal drainage by magnesium sulfate and on rereading the slides five years later, the cellular entities were still perfectly preserved as to contour, shape and staining qualities.

This volume in its limited sphere, will undoubtedly bring forth controversial repercussions and thus stimulate further efforts.



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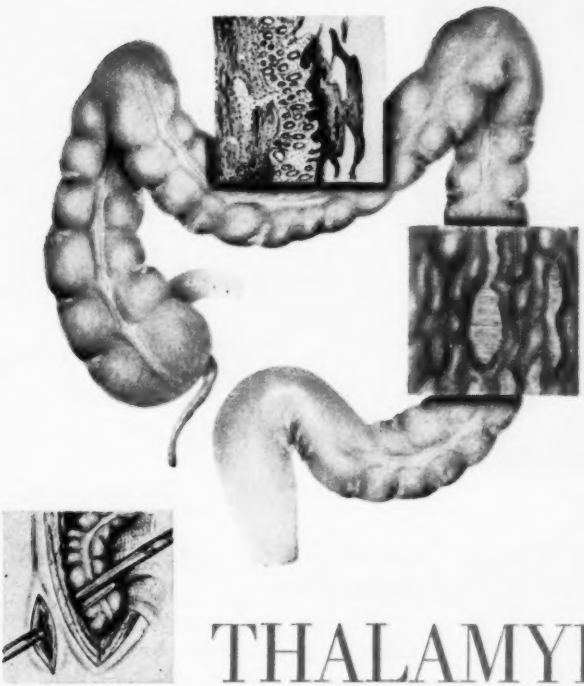

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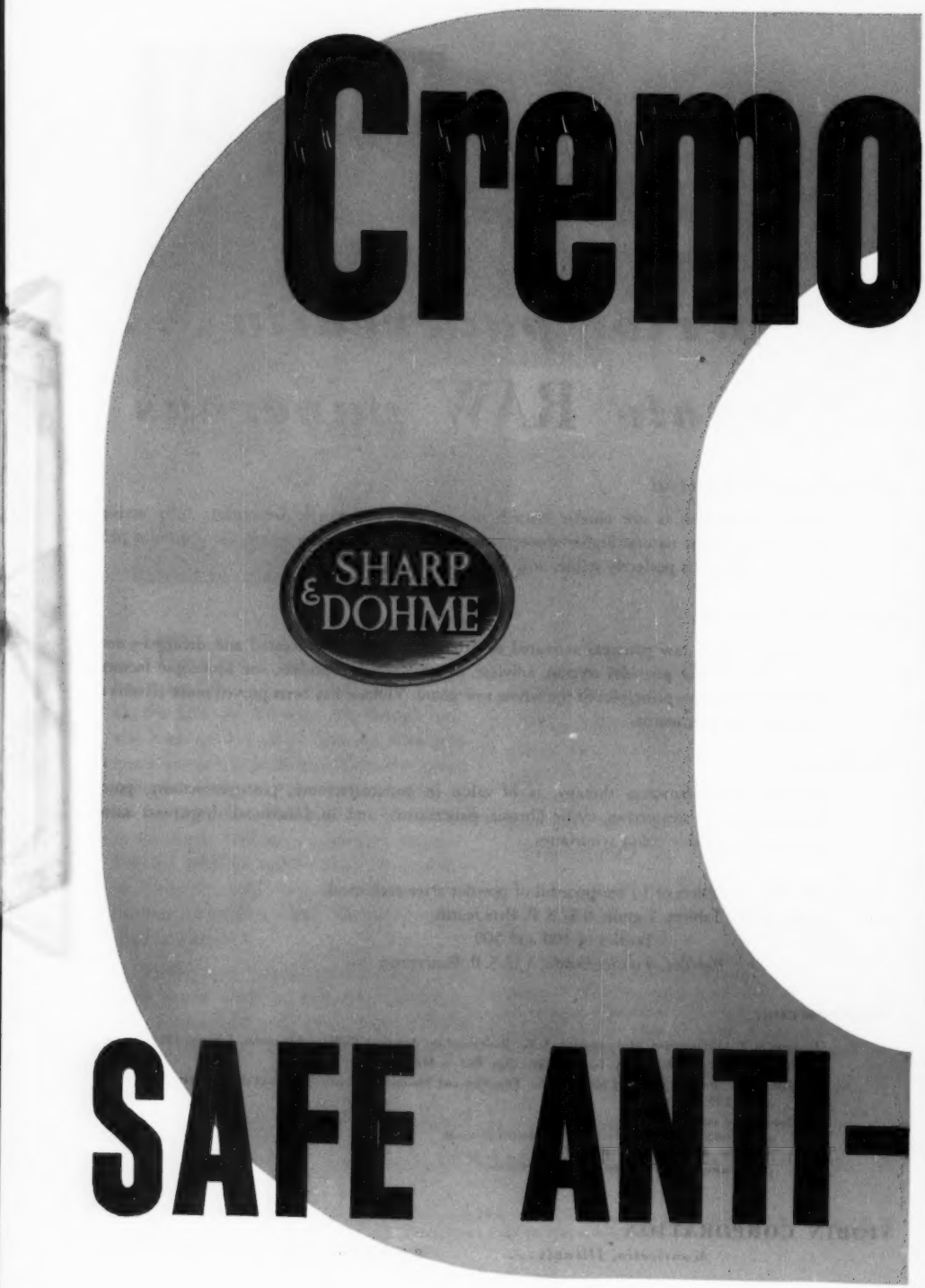
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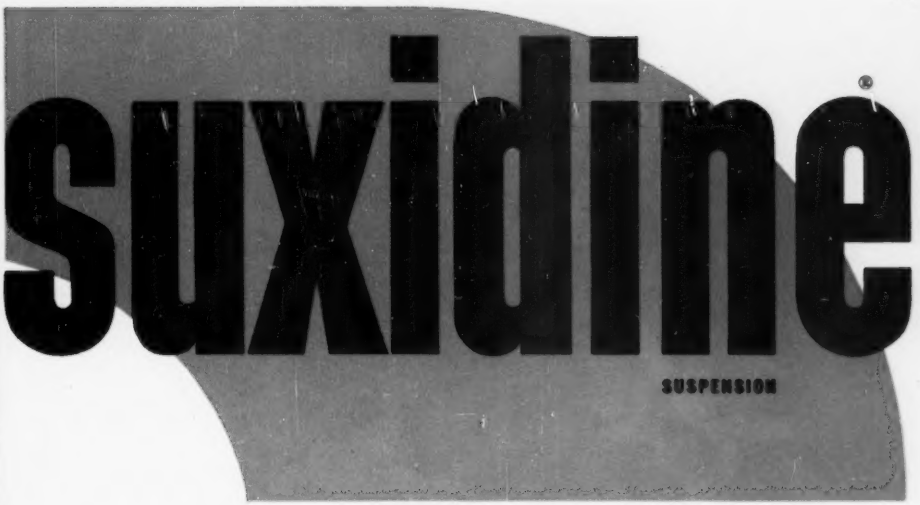


CREMOSUXIDINE® is a smooth, delicious, chocolate-mint flavored suspension of SULFASUXIDINE®—the virtually nontoxic intestinal bacteriostat—with detoxicant kaolin and pectin for control of infectious and non-specific diarrheas. Since SULFASUXIDINE remains in high concentration in the intestines and is only sparingly absorbed, CREMOSUXIDINE is sound, effective therapy for diarrhea, even in infants and children. Supplied in SPASAVER® bottles of 16 fluidounces. Sharp & Dohme, Philadelphia 1, Pennsylvania.

bile should be brisk business

not cholagogue
not choleretic
but hydrocholeretic

In nonobstructive biliary disease, stimulation of a large volume of bile with a high water content for copious flushing of the biliary tract is essential. To complement the hydrocholeresis, biliary duct and sphincter of Oddi relaxation is vital. Cholan-HMB contains dehydrocholic acid (250 mg. or 3¾ gr. per tablet)—the most potent, least toxic hydrocholeretic known. It also contains the safe, selective spasmolytic, homatropine methylbromide (2.5 mg. or 1/24 gr.)—with phenobarbital (8 mg. or 1/8 gr.).

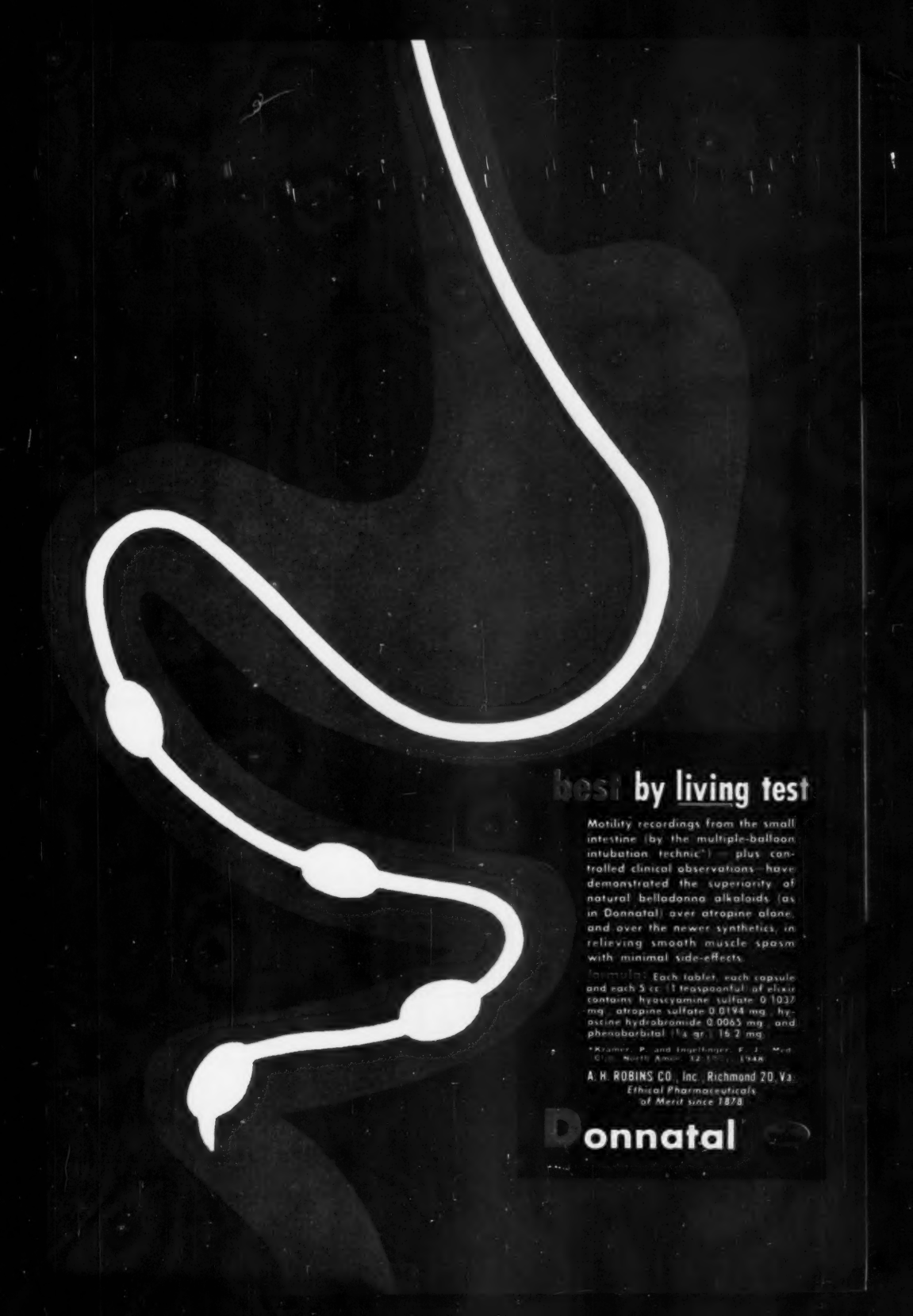
MALTBIE ... *first*

to develop American process for converting crude viscous ox-bile into chemically pure dehydrocholic acid.

Chart shows increase in biliary secretion after injection of sodium dehydrocholate, as compared to various bile salts.

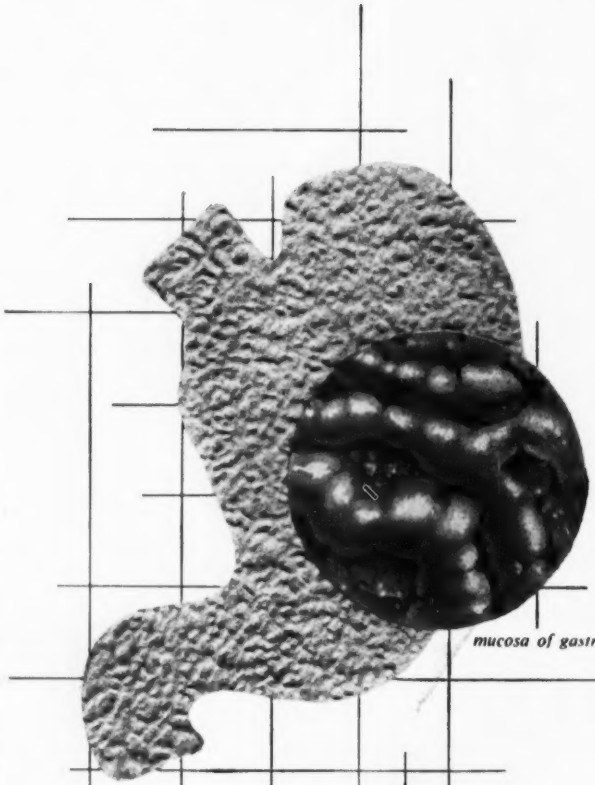
MALTBIE LABORATORIES, INC., NEWARK 1, N. J.

Cholan *hmb*


best by living test
Motility recordings from the small intestine (by the multiple-balloon intubation technic*) — plus controlled clinical observations — have demonstrated the superiority of natural belladonna alkaloids (as in Donnatal) over atropine alone, and over the newer synthetics, in relieving smooth muscle spasm with minimal side-effects.
Formula: Each tablet, each capsule and each 5 cc. (1 teaspoonful) of elixir contains: hyoscyamine sulfate 0.1037 mg., atropine sulfate 0.0194 mg., hyoscine hydrobromide 0.0065 mg., and phenobarbital (1/4 gr.) 16.2 mg.
*Kramer, P. and Ingelfinger, F. J. Med. Clin. North Amer. 32:1701, 1948.
A. H. ROBINS CO., Inc., Richmond 20, Va.
Ethical Pharmaceuticals of Merit since 1878
Donnatal

for

gastritis



mucosa of gastritis

maalox®

Suspension Maalox-Rorer is a colloidal suspension of the *hydroxides* of Magnesium and Aluminum. It is pleasant to taste. Continuous clinical use has demonstrated that it causes a *quick satisfactory relief* of pain and discomfort caused by gastritis.

The dose is two to four fluidrachms.

supplied: In 355 cc. (12 fluidounce) bottles. Also in tablets (Each Maalox tablet is equivalent to one fluidrachm of Suspension). *Samples will be sent promptly on request.*

WILLIAM H. RORER, INC.

Drexel Bldg., Independence Square

Philadelphia 6, Penna.

Rubragran gives your patient

		1 CAPSULE:	1 CAPSULE T.I.D.
VITAMIN B_{12}		25 mcgm.	75 mcgm.
FOLIC ACID		1.67 mg.	5 mg.
IRON	(elemental)	67 mg.	200 mg.
	as ferrous sulfate exsic.	230 mg.	690 mg.
	equiv. to ferrous sulfate U.S.P.	300 mg. (5 gr.)	900 mg. (15 gr.)
ASCORBIC ACID		100 mg.	300 mg.
DESICCATED LIVER (stabilizing agent)		100 mg.	300 mg.

1 Capsule t.i.d.

Bottles of 100 and 500

When you want to give the patient more than just iron alone...

RUBRAGRAN

Squibb Therapeutic Hematinic

SQUIBB

your patient
will not tire
of taking...

TĪTRALAC

TRADEMARK

[GLYCINE AND CALCIUM CARBONATE]

an effective antacid

continuously acceptable

TĪTRALAC's "just right" mint flavor and smooth texture ensure continuous acceptance.

acts like milk

TĪTRALAC's precise proportions of glycine and calcium carbonate provide a buffering action singularly like that of whole milk.

No systemic alkalosis or acid rebound... free from acid-generating sugars. Especially useful in milk-sensitive patients or where weight gain is undesirable.

available in 3 forms

TĪTRALAC* Tablets..... Boxes of 40, bottles of 100 and 1000
TĪTRALAC Powder..... Jars of 4 oz.
TĪTRALAC Liquid.. Bottles of 8 fl. oz.

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LAWRENCEBURG, INDIANA